Hilkka Ylihärsilä

Early Growth and Adult Health: Focus on Blood Pressure, Glucose Tolerance Status and Body Composition

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Department of Health Promotion and Chronic Disease Prevention
National Public Health Institute
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Department of Public Health
University of Helsinki, Finland

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FOCUS ON BLOOD PRESSURE, GLUCOSE TOLERANCE STATUS AND BODY COMPOSITION

A C A D E M I C D I S S E R T A T I O N

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ABSTRACT

Background. Theory of developmental origins of adult health and disease proposes that experiences during critical periods of early development may have consequences on health throughout a lifespan. Circumstances *in utero* or during infancy may induce changes in body size and structure, metabolism, hormone secretion and gene expression. These changes may serve as advantageous adaptations aiming at better survival if environmental conditions, such as nutrient availability, remain as predicted in early life. If the predictions, however, mismatch with reality, these adaptations may lead to increased susceptibility to disturbances in adult health. Low birth weight in subjects born at term is a widely used crude indicator of adjustments during fetal life that are unfavourable in an affluent society. The aim of these studies was to characterize the associations between early growth and some components of the metabolic syndrome cluster, and factors that may contribute to and interact with these associations.

Subjects and methods. Participants of these studies belong to clinically examined subsets of two epidemiological cohorts with data on birth measurements and, for the younger cohort, on serial recordings of weight and height during childhood. They were born as singletons between 1924-33 and 1934-44 in the Helsinki University Central Hospital, and 500 and 2003 of them, respectively, attended clinical studies at the age of 65-75 and 56-70 years, respectively. Their clinical examinations included an oral glucose tolerance test, blood pressure (BP) measurements, an analysis of body composition by bioelectrical impedance, questionnaires on medication and exercise habits, and determination of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 (PPARγ2) gene.

Results. In the 65-75 year old men and women, the inverse relationship between birth weight and systolic BP was confined to people who had established hypertension. Among them a 1-kg increase in birthweight was associated with a 6.4-mmHg (95% CI: 1.0 to 11.9) decrease in systolic BP. This inverse relationship was further confined to people with the prevailing Pro12Pro polymorphism of the PPARγ2 gene (9.3 mmHg/kg, 95% CI: 2.1-16.4). Low birth weight was related to the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEI/ARB, p=0.03). Again, this association interacted significantly with the PPARγ2 gene polymorphism, the carriers of

the Pro12Pro with low birth weight being more likely to receive ACEI/ARB treatment (p=0.01 for interaction).

A lower rate of glucose intolerance was related to habitual frequent or moderate leisure-time exercise. This effect was dependent on birth size, being strongest among those with a small body size at birth. Among subjects with birth weight ≤3000 g, the odds ratio (OR) for glucose intolerance was 5.2 (95% CI: 2.1 to 13) in those who exercised less than 3 times per week compared to regular exercisers; in those who scored their exercise light compared with moderate exercisers (defined as comparable to brisk walking) the OR was 3.5 (1.5 to 8.2).

In the 56-70 year old men a 1 kg increase in birth weight corresponded to a 4.1 kg (95% CI: 3.1 to 5.1) and in women to a 2.9 kg (2.1 to 3.6) increase in adult lean mass. Height-normalized indices of adult lean and fat body mass (LMI, lean mass/height squared and FMI, fat mass/ height squared) were used in the analyses of associations of body mass index (BMI) at birth and change in BMI during four periods of childhood growth with adult body composition. Adult LMI was positively associated with BMI at birth (0.24 and 0.20 kg/m^2 higher for each 1 SD increase in BMI at birth in men and in women, respectively). Rapid growth, i.e. crossing from an original BMI percentile to a higher one, was positively related to adult LMI during all growth periods analysed: rapid gain in BMI between birth and 1 year of age, 1-2, 2-7 and 7-11 years resulted in men to a 0.17, 0.21, 0.44 and 0.32 kg/m^2 and in women to a 0.22, 0.20, 0.46 and 0.26 kg/m^2 higher adult LMI, respectively. FMI and percent body fat were positively associated with rapid gain in BMI between 2 and 11 years of age.

Conclusions. These studies suggest that in the 65-75 year old subjects the well-known inverse association between birth weight and systolic BP becomes focused in hypertensive people because pathological features of BP regulation, associated with slow fetal growth, become self-perpetuating in adult life and are amplified by age. Insulin resistance of the Pro12Pro carriers with low birth weight may interact with the renin-angiotensin-aldosterone system leading to raised BP levels. Subjects predisposed to type 2 diabetes due to their low birth weight are strongly protected from glucose intolerance by regular exercise at a moderate intensity. In the 56-70 year old subjects rapid gain in BMI before the age of 2 years increased adult lean body mass without excess fat accumulation whereas rapid gain in BMI during later childhood, despite the concurrent rise in lean mass, resulted in relatively higher increase in adult body fat mass. These findings illustrate how genes, the environment and their interactions, early growth patterns, and adult lifestyle modify adult health risks which originate from early life.

Keywords: birth weight, blood pressure, body composition, cohort studies, developmental origins, epidemiology, exercise, insulin resistance, peroxisome proliferator-activated receptor-γ2 gene polymorphism, type 2 diabetes

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TIIVISTELMÄ

Elämänkaarinäkökulman mukaan aikuisiän terveydentilan tai sairauksien alkuperä voi löytyä jo varhaiskehityksestä. Sikiöaikana tai varhaislapsuudessa kehityksen kriittisen vaiheen tulevaisuutta ennakoivat olosuhteet voivat aiheuttaa myöhempään menestymiseen tähtääviä sopeutumismuutoksia kehon ja elinten koossa ja kasvussa, rakenteessa, aineenvaihdunnassa, hormonaalisessa toiminnassa tai geenien ilmentymisessä. Jos ennuste esimerkiksi ravinnon riittävyydestä ei vastaakaan todellisuutta, tapahtuneet muutokset voivat altistaa häiriöille aikuisiän terveydentilassa. Pientä syntymäpainoa täysiaikaisina syntyneillä on yleisesti käytetty vauraassa nyky-yhteiskunnassa epäedullisen kehityksen osoittajana. Väitöskirjatutkimusten tavoitteena oli luonnehtia tarkemmin sekä yhteyksiä syntymäkoon tai lapsuuskasvun ja aikuisiän metabolisen oireyhtymän osatekijöiden välillä että näihin yhteyksiin myötä- tai vuorovaikuttavia tekijöitä.

Tutkittavat ja menetelmät. Tutkimuksiin osallistuneet miehet ja naiset kuuluvat kahteen vuosina 1924-33 ja 1934-44 Helsingin yliopistollisen sairaalan Naistenklinikalla syntyneeseen epidemiologiseen kohorttiin, joista on kerätty syntymän aikaiset tiedot kuten paino- ja pituusmitat. Nuoremmasta kohortista on käytettävissä lisäksi lapsuudenaikaisia seurantamittauksia. Vanhemmasta kohortista tutkittiin kliinisesti 500 henkilöä 65-75 vuoden iässä ja nuoremmasta 2003 henkilöä 56-70 vuoden iässä. Kliinisiin tutkimuksiin sisältyi oraalinen sokerirasitus, verenpainemittauksia, kehon koostumuksen mittaus bioelektrisellä impedanssilla, kyselyt lääkityksestä ja liikuntatottumuksista, ja peroksisomiproliferaattoreilla aktivoituvan reseptori-γ2 (PPARγ2) geenin Pro12Ala-polymorfismin määritys.

Tulokset. 65-75 vuotiailla miehillä ja naisilla tunnettu käänteinen yhteys systolisen verenpainetason ja syntymäpainon välillä löytyi vain niiltä, joilla oli todettu verenpainetauti. Heillä 1 kg korkeampi syntymäpaino vastasi 6.4 mmHg (95% luottamusväli: 1.0-11.9) matalampaa systolista verenpainearvoa. Edelleen tämä yhteys todettiin vain niillä verenpainetautia sairastavilla, joilla oli PPARγ2-geenin vallitseva Pro12Pro-muoto (9.3 mmHg/kg, 95% CI: 2.1-16.4). Matala syntymäpaino liittyi angiotensiini-1-konvertaasin estäjien ja angiotensiinireseptorin salpaajien runsaampaan käyttöön (p=0.03). Myös tällä yhteydellä oli merkittävä interaktio PPARγ2-geenin

polymorfismin kanssa: pienipainoisina syntyneistä vain Pro12Pro-muodon kantajilla nämä lääkkeet olivat useammin käytössä (interaktion p=0.01).

Säännöllisesti tai kohtalaisella teholla vapaa-ajan liikuntaa harrastavilla vanhemman kohortin jäsenillä esiintyi vähemmän sokerinsietokyvyn heikentymistä. Tämä ilmiö oli vahvin pienikokoisina syntyneillä. Jos syntymäpaino oli alle 3000 g, heikentyneen sokerinsietokyvyn kerroinsuhde (odds ratio, OR) oli 5.2 (95% luottamusväli: 2.1-13) harvemmin kuin 3 kertaa viikossa liikkuvilla verrattuna useammin liikkuviin; vain kevyttä liikuntaa harrastavilla OR oli 3.5 (1.5 - 8.2) verrattuna teholtaan vähintään reipasta kävelyä vastaavaa liikuntaa harrastaviin.

56-70-vuotiailla 1 kg suurempi syntymäpaino vastasi miehillä 4.1 kg (95% luottamusväli: 3.1-5.1) ja naisilla 2.9 kg (2.1-3.6) suurempaa rasvatonta painoa. Lapsuuden painoindeksin kehityksen ja aikuisiän kehon koostumuksen välisiä yhteyksiä tutkittaessa käytettiin aikuispituudella korjattuja rasvattoman ja rasvamassan indeksejä (LMI, rasvaton paino/m^2 ja FMI, rasvamassa/m^2). Aikuisiän LMI oli sitä suurempi mitä korkeampi oli syntymämitoista laskettu painoindeksi (BMI), tai jos kasvoi lapsuusaikana nopeasti eli siirtyi BMI-käyrästöllä ylemmäksi minkä tahansa tutkitun neljän kasvuvaiheen (0-1, 1-2, 2-7 ja 7-11 v) aikana. Aikuisiän FMI ja kehon rasvaprosentti olivat positiivisesti yhteydessä nopeaan BMI-kasvuun vasta toisen ikävuoden jälkeen.

Päätelmät. Näiden tutkimusten mukaan 65-75 vuotiailla henkilöillä tunnettu yhteys syntymäpainon ja systolisen verenpaineen välillä keskittyy verenpainetautiin jo sairastuneisiin. Löydös viittaa siihen, että huonoon sikiöaikaiseen kasvuun liittyvät verenpaineen säätelyn patologiset piirteet muuttuvat aikuisiällä itseään ylläpitäviksi ja vahvistuvat iän myötä johtaen verenpainetautiin. Pienipainoisina syntyneiden Pro12Pro-geenimuodon kantajien insuliiniresistenssin vuorovaikutus reniini-angiotensiini-aldosteroni-systeemin kanssa voi myötävaikuttaa kohonneeseen verenpainetasoon. Säännöllinen tai teholtaan vähintään reipasta kävelyä vastaava liikunta suojaa sokerinsietokyvyn heikkenemiseltä erityisesti niitä, joilla on suurentunut riski sairastua tyypin 2 diabetekseen pienen syntymäpainon takia. 56-70 vuotiailla henkilöillä nopea BMI:n kasvu ennen kahden vuoden ikää johti suurempaan aikuisiän rasvattomaan painoon ilman rasvamassan kasvua, kun taas nopea BMI-nousu myöhemmän lapsuuden aikana johti samanaikaisesta rasvattoman painon lisääntymisestä huolimatta suhteellisesti suurempaan rasvamassan lisääntymiseen. Nämä löydökset kuvaavat sitä, kuinka geenit ja ympäristö keskinäisine vuorovaikutuksineen, varhainen kasvu ja aikuisiän elintavat muuntelevat varhaiskehityksestä juontuvia aikuisiän terveysriskejä.

Asiasanat: syntymäpaino, verenpaine, kehon koostumus, kohorttitutkimus, elämänkaari, epidemiologia, liikunta, insuliiniresistenssi, peroksisomiproliferaattoreilla aktivoituvan reseptori - γ2 (PPARγ2) geenin polymorfismi, tyypin 2 diabetes

CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACEI	Angiotensin converting enzyme inhibitor
Adiposity rebound	Point at which childhood BMI increases after its nadir
ARB	Angiotensin receptor blocker
BIA	Bioelectrical impedance analysis
BP	Blood pressure
BMI	Body mass index, weight/height^2
CHD	Coronary heart disease
CVD	Cardiovascular disease
FMI	Fat mass index, fat mass/ height^2
GH	Growth hormone
HPA-axis	Hypothalamic-pituitary-adrenal axis
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
IGF	Insulin-like growth factor
IOTF	International Obesity Task Force
LMI	Lean mass index, lean mass/height^2
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
OR	odds ratio
PPARγ2	Peroxisome proliferator-activated receptor-γ2
Ponderal index	Weight at birth/(length at birth)^3
SD	Standard deviation
SGA	Small for gestational age
β	Regression coefficient

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Ylihärsilä H, Eriksson JG, Forsén T, Kajantie E, Osmond C, Barker DJ. Self-perpetuating effects of birth size on blood pressure levels in elderly people. Hypertension 2003; 41(3): 446-50.

II Ylihärsilä H, Eriksson JG, Forsén T, Laakso M, Uusitupa M, Osmond C, Barker DJ. Interactions between peroxisome proliferator-activated receptor-gamma 2 gene polymorphisms and size at birth on blood pressure and the use of antihypertensive medication. Journal of Hypertension 2004; 22(7): 1283-7.

III Eriksson JG, Ylihärsilä H, Forsén T, Osmond C, Barker DJ. Exercise protects against glucose intolerance in individuals with a small body size at birth. Preventive Medicine 2004; 39(1): 164-7.

IV Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJ, Eriksson JG. Birth size, adult body composition and muscle strength in later life. International Journal of Obesity (Lond) 2007; 31(9): 1392-9.

V Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJP, Eriksson JG. Body mass index during childhood and adult body composition in men and women aged 56 to 70 years. American Journal of Clinical Nutrition 2008; 87(6): 1769-75

1 INTRODUCTION

The developmental origins of adult health and disease theory has been developed on the basis of David Barker's epidemiological findings in 1980's and experimental studies on animals (1). According to this theory, experiences during critical periods of early development may have consequences on health throughout a lifespan. This phenomenon is called programming. Changes in body and organ size and structure, metabolism, settings of the hormonal axes, and gene expression, created by restricted growth or other insults *in utero* and in infancy, may serve as advantageous adaptations aiming at better survival if the restrictive environmental conditions, such as nutrient availability, remain meagre in childhood and in later life. In times of plenty, however, these adaptations may lead to increased susceptibility to adult diseases.

Metabolic syndrome is a clustering of cardiometabolic risk factors. It includes major health outcomes, e.g. glucose intolerance, elevated blood pressure and abdominal obesity (2; 3). These are all linked to low birth weight which, across the whole range of normal birth weights in term infants, is a widely used crude indicator of unfavourable adjustments to rich societies during fetal life. The epidemiologic evidence of these associations is abundant but raises the question of how, and through what mechanisms, this programmed propensity to diseases develops and is modified during the life course. Experimental studies in animals provide one approach to investigate this, but demonstration of these processes in humans is more complicated.

The aim of the present study was to move from previous, mostly descriptive studies towards studies focusing on the importance of interactive or additive effects of early growth, genetic and socioeconomic factors, and adult lifestyle as the potential mechanisms affecting the association between early growth and some components of the metabolic syndrome in adult life. This research project is a part of a clinical epidemiological study of 15846 subjects, the Helsinki Birth Cohort Study ("IDEFIX-study"). Information on childhood growth and development has been obtained from birth, child welfare and school health care records. Information on adult health, lifestyle and socioeconomic factors has been obtained from national registers, census-data, questionnaires and a clinical study of 2503 subjects, who comprise the thesis study population.

2 REVIEW OF THE LITERATURE

2.1 Developmental origins of adult health and disease

The hypothesis of the developmental component of subsequent adult diseases was brought to broader attention by epidemiological studies by David Barker and colleagues in the 1980's, showing an inverse relationship between birth size and disease prevalence or risk factors in later life (4-8). Whereas the interplay between genetic and adult lifestyle influences in the development of diseases has long been acknowledged, the concept that subtle experiences at the beginning of the lifecycle have a substantial effect on later disease risk has opened an entirely new field for research during the last two decades.

The theory was at first criticized: the relationships between poor early growth and adult disease were suggested to be explained by confounding factors such as selection, recall or publication bias, cohort effect, duration of gestation and socioeconomic conditions, or lifestyle throughout lifecycle (9-11). Accumulating evidence from several populations worldwide has, however, confirmed the original epidemiological findings of the relationship between birth size and major public health outcomes, including blood pressure (12), cardiovascular disease (13-18) and type 2 diabetes (19; 20), while recent studies of early growth associations have expanded research to several other disorders such as osteoporosis (21), depression (22-24) which in itself, interestingly, has been linked with metabolic disturbances (25; 26), schizophrenia (27; 28), autoimmune diseases (29), respiratory function (30) and cancers (31; 32).

Since these relationships between birth size and adult disease are independent of gestational age, small birth size represents poor fetal growth rather than prematurity. However, programming is not confined only to subjects with low birth weight, rather the effects operate across the whole range of birth weights. The early development of twins differs from that of singletons, and although twin studies are utilized in the research on this field, the present review will focus on studies on singletons.

The hypothesis is also supported by data from prospective clinical investigation and animal experiments (1; 33). Actually, in several animal species the concept of environmental programming has long been accepted: a given genotype can produce several phenotypes depending on environmental influences during early growth. For example, as early as 1875, the color of a specific butterfly was demonstrated to depend on temperature (34); the sex of turtles and crocodilians is determined by

temperature during hatching (35; 36). These studies have also highlighted the existence of sensitive periods, so called critical windows, during which an influence may cause a persistent effect. Timing of these early experiences is crucial also in humans: the response to the same environmental factor may differ according to the stage of development (35-39).

Responses to environmental influences during early growth, that determine some of the characteristics of adults, have been suggested to be classified according to the nature of the response (40). Developmental plasticity should be distinguished from developmental disruption, e.g. gross events causing irreversible damage such as medication with thalidomide during pregnancy, and from immediately adaptive responses promoting immediate survival with long-term consequences such as redistribution of blood flow to vital organs under low oxygen conditions (40). Obviously, these processes overlap, but developmental plasticity, the range and degree of adaptations in physiological homeostatic mechanisms that a fetus or infant makes in response to environmental clues during critical windows, aims to guarantee the ability to thrive and reproduce successfully in future circumstances that are forecasted by the conditions *in utero* or in early infancy. If this forecast proves to be incorrect because of misinterpretation or change in environment, the adaptations mismatch with the subsequent reality and may predispose the individual to greater health risks, such as disturbances in glucose tolerance, blood pressure regulation and the cardiovascular system, that manifest in later life.

Originally named 'Fetal origins of adult disease' with emphasis on thrifty phenotype because of intrauterine deprivation, the new terminology reflects the increased knowledge on developmental plasticity covering the period from (pre)conception to infancy and childhood during which events may induce lifelong consequences on the capacity to cope with environment in adult life. In many studies the association between birth weight and adult outcome was found or strengthened after adjustment for adult size, and Lucas et al. directed attention to the role, whether independent or interactive, of change in size between birth and adulthood (41). The framework is further expanding towards genetic effects, epigenetic silencing of gene expression via DNA methylation, and intergenerational effects as underlying and modifying factors behind the recognized associations (42-46). All these factors and their interactions, that establish resilience or susceptibility to later environmental stressors including lifestyle, can be viewed from a lifecourse concept (Figure 1, reprinted with permission from Kajantie 2003 (47)).

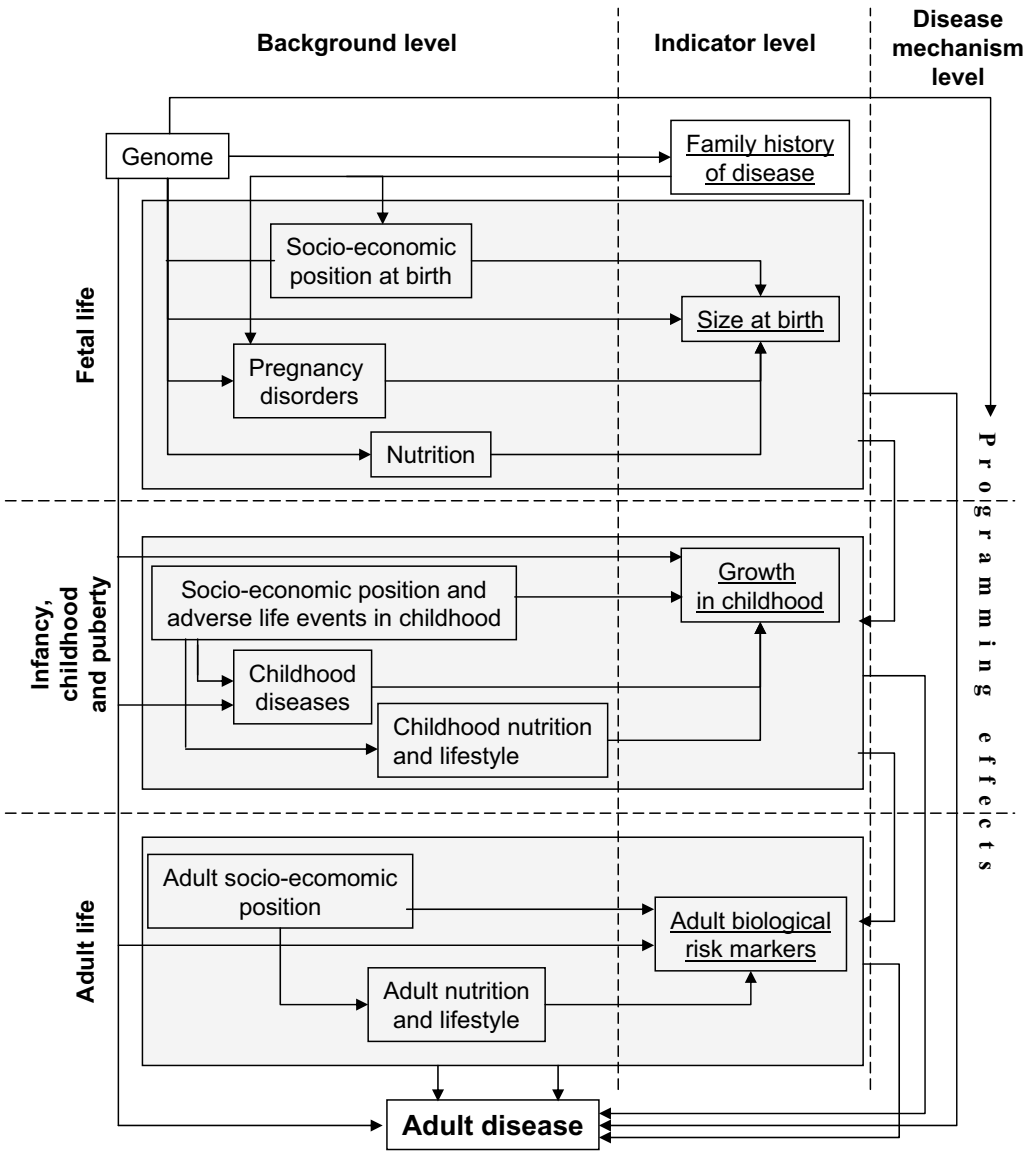

Figure 1. The lifecourse concept for fetal, childhood and adult effects on health in adulthood. The effects of an individuals family history, (epi)genome and susceptibility factors throughout life may interact, e.g. vulnerability to an adverse lifestyle may vary by a given genetic polymorphism or by adverse experiences during growth. The latter may be indicated as e.g. small birth size or slow growth rate during childhood. Reprinted with permission from Kajantie 2003 (42).

2.2 Characteristics of growth in early life

2.2.1 Periods of growth

Human growth consists of three partly overlapping periods: 1) the rapid fetal growth period that continues into infancy; 2) the childhood growth; and 3) the growth spurt in puberty (48). Growth during the early fetal period consists mainly of increase in cell numbers, hyperplacia, while increase in cell size, hypertrophy, gradually takes over. Apart from cell divisions and hypertrophy, cell differentiation, migration, interaction with other cells and organs, and apoptosis are essential in completing the growth process. After the growth period, a majority of cell types undergo constant renewal but the ability to grow is limited and occurs mostly by means of increase in cell size.

The role of growth-regulating hormones and other growth factors varies according to the growth phase. Among other factors, insulin and insulin-like growth factors are significantly involved in fetal and infant growth whereas growth during childhood is largely dependent on growth hormone and thyroxine (49). In puberty the important influence of growth hormone is joined by sex hormones. The nuances of growth regulation remain partly unresolved.

Most of the growth, relatively, occurs in the fetal period, during which the highest growth rate is approximately tenfold compared to the growth rate in mid-childhood (Figure 2) (47). Linear growth, e.g. rate of length gain, is greatest at approximately 20 week of gestation, and rate of weight gain at 34 weeks. During rapid growth the fetus is most vulnerable to environmental influences.

These characteristics of growth, i.e. the restricted duration of the growth phase combined with the highest growth rates *in utero*, illustrate the large potential of lifelong consequences if growth is disturbed during early life. The timing and nature of the influence, e.g. lack of nutrients, determines the pattern of the response, the complexity of which may further vary by other factors such as genotype and gender (50; 51).

2.2.2 Determinants of birth size

Small birth size is, because of its availability, widely used in studies assessing the effects of early growth on later health, although it is an imprecise and crude marker of an adverse intrauterine environment. Naturally, some small babies have not experienced any growth restriction but are genetically small, representing the lower tail of the normal birth weight distribution. Correspondingly, a part of growth-

restricted babies fall into the category of normal weight babies because of their greater genetic growth potential. Nevertheless, up to 45% of variance in birth weight has been estimated to be due to effects of uterine environment, with fetal genome explaining 10-15%, maternal fixed features including genes explaining 25%, and maternal factors varying from pregnancy to pregnancy explaining 20% of the variance.

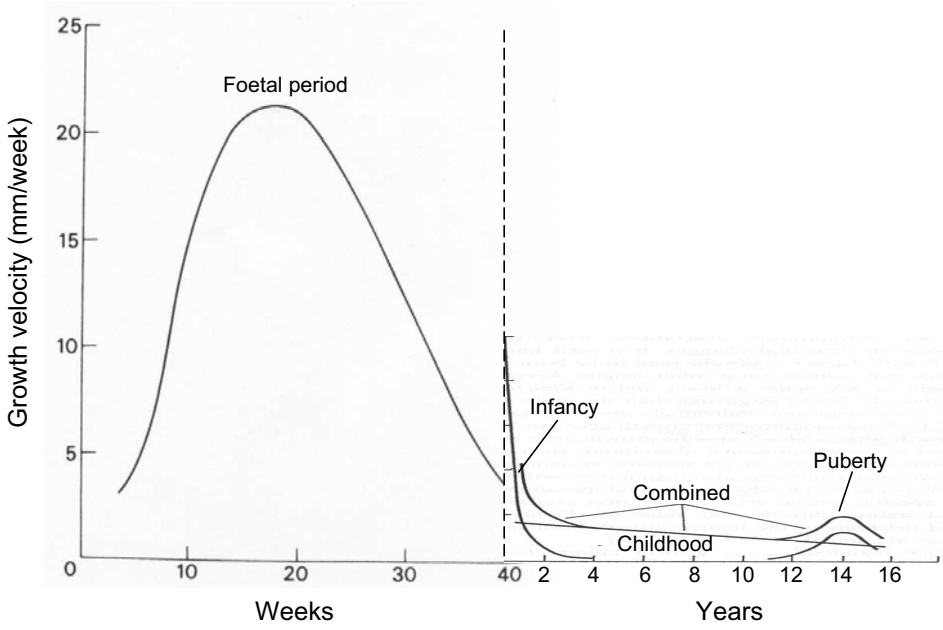

Figure 2. Growth velocity throughout the human growth period. The scale of the Y axis is the same for both parts of the figure, illustrating the high growth rate during the fetal period compared with postnatal life. Reprinted with permission from Kajantie 2003 (42).

A number of endocrine, nutritional, socioeconomic, behavioral (e.g. maternal smoking) and other factors have an impact on birth size. Most of these, such as the effect of paternal size and the sex of the fetus, can be traced to the genome of the fetus, whereas others such as parity and maternal size represent the degree of maternal constraint. In general, the genome of the fetus determines fetal growth until restricted by maternal and uteroplacental conditions, i.e. maternal constraint. These growth-limiting processes act e.g. by limiting nutrient supply or by re-setting the metabolic-hormonal axes that regulate growth (52). Physiological maternal constraint acts in all pregnancies and is greater by younger maternal age, smaller maternal size and primi- or multiparity (53-55). Pathological processes, such as placental defects, may further enhance the constraint. The mechanisms of maternal constraint are poorly researched but probably involve the response of the uteroplacental vessels to pregnancy, imprinting of genes, transgenerational effects and maternal diet (1; 52; 56). In addition, birth size is obviously largely dependent on the duration of gestation.

2.2.3 Rate of postnatal growth in relation to later health

Genetically set growth trajectory determines growth potential (57). Periods of impaired growth, due to environmental reasons, are followed by accelerated growth until the original inherited growth path is reached. This is evident in infants born small for gestational age: 90% of them show postnatal catch-up growth in weight, height and BMI, defined as centile crossing on standard growth charts (58-60). This is usually evident by 6 months of age. Regression to the mean explains only a small degree of the catch-up and catch-down phenomena. Of all infants, approximately one-quarter show catch-up growth, while half follow the same weight or length centile position from birth (60). However, not all growth deficits due to environmental exposures, such as poor nutrition or maternal pregnancy smoking, are compensated during later growth (61; 62).

Catch-up growth -hypothesis suggests that the crucial feature of the development of long-term consequences of restricted fetal growth is the early postnatal growth rate (41; 63). Traditionally slow postnatal growth of infants born small has been interpreted as detrimental in the short-term context of failure to thrive, with emphasis on malnutrition or food deprivation and cognitive development in childhood. There is little evidence on associations between childhood growth rate and health in adulthood, but recent findings in the Helsinki cohort showed that slow gain in weight or BMI between birth and 2 years of age was associated with coronary heart disease and its risk factors including type 2 diabetes (64; 65). However, the potential benefits of growth promotion in infancy or early childhood

have been contradicted: in younger populations, some of those born preterm or small for gestational age, rapid postnatal growth has been linked with risk factors of cardiovascular disease (66-70). In adults, a rapid gain in weight or BMI during later childhood, after impaired fetal and infancy growth, has increased the risk of type 2 diabetes and coronary heart disease (64; 65; 71). Despite the discrepancies of its timing during childhood, postnatal high rates of growth in subjects born small also seem to be crucial for blood pressure levels (72-74). Some studies suggest that the type of growth, whether linear or ponderal, is essential in the development of growth-rate related adult health risk factors and outcomes (73; 75; 76).

To sum up, from the life-course perspective, a period of poor growth *in utero* or early infancy followed by rapid growth may increase susceptibility to metabolic disorders most. On the other hand, a specific postnatal growth pattern might reverse the effects of fetal programming. The potential public health impact of this approach is considerable because growth in infancy and childhood is more amenable to interventions than that of a fetus. Nevertheless, longitudinal studies are needed to explore the long-term outcomes of different growth rates at several periods of growth before any nutritional or other interventions to regulate growth can be recommended. Unfortunately this type of confirmation takes decades; meanwhile cross-sectional studies with data on childhood growth and adult outcomes may offer important information. However, the interpretations of growth data are further complicated because there is no single recommended statistical method to measure and analyze growth patterns. For example, different definitions of slow gain in weight or BMI in childhood have been shown to identify different populations with different profiles (77).

2.3 Mechanisms of programming

Hales and Barker referred to individuals with bodies and metabolism adapted to a low level of nutrition as having a “thrifty phenotype” (78). Nutritional signals are, indeed, likely to have a key role in initiating programming (1; 79). This is purposeful also from an evolutionary framework: in a deprived environment reproduction of individuals adapted to low caloric intake is presumably more successful, promoting species survival through transient changes in the environment (33; 52). However, if the signals during fetal life about expected environment are erroneous or inaccurate because of maternal disease, placental dysfunction or change in environmental conditions after birth, such as nutritional improvement in developing societies, the fetus is predisposed to an increased disease risk in later life. In rich modern societies the discrepancy between prenatal nutritional supply,

limited by physiological maternal constraint, and postnatal abundant nourishment is great even without any adverse experiences *in utero*.

Numerous animal experiments support the importance of nutrient supply in programming (1; 80; 81). The fetal programming of e.g. hypertension has been modeled in several species mostly by subjecting dams to undernutrition during pregnancy (80). Offspring of these pregnancies develop hypertension and other features linked to insulin resistance (80). In humans the best evidence of *in utero* undernutrition in the development of adult glucose intolerance, cardiovascular disease and hypertension comes from studies on men and women exposed to wartime famine during the Dutch Hunger Winter while *in utero* (37; 38; 82; 83). On the other hand, these studies have also shown that restricted maternal nutrition is not synonymous with reduced offspring birth size; the latter may be related with an adult outcome while the former is not (84; 85). However, in contrast to the Dutch studies, maternal exposure to extreme undernutrition during the siege of Leningrad could not be associated with offspring outcome (86). Since the duration of the Dutch famine was relatively short and clear-cut, 5 months, while in Leningrad exposure to food shortage may have continued into infancy and even later childhood, the different level of postnatal nutrition and growth might provide one explanation.

Whatever the initiating event, nutritional or other, it may trigger several possible mechanisms that eventually lead to increased susceptibility to adult diseases. The fetus may respond to the trigger by sustained metabolic, neuroendocrine or structural changes. The degree and variety of these changes and vulnerability or resilience depend on its developmental stage and genome. Figure 3 presents a framework of suggested mechanisms for the biological basis of the associations between fetal experiences and adult health outcomes (87).

Among the mechanisms, alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis are likely to play an essential role (88-93). Permanently changed set-points of the HPA-axis together with changes in the sympathoadrenal system, which also mediates the stress response, may affect metabolism and the vasculature in a way that predisposes to e.g. insulin resistance and hypertension (51; 94; 95). There is evidence of exaggerated BP or cortisol response to stress in offspring that is related to maternal nutrition (92; 96). Several pathways to a single outcome are possible: essential hypertension has also been proposed to be a consequence of a reduced nephron number which increases susceptibility to progressive glomerular injury and thus progressively rising blood pressure (97; 98). In line with this hypothesis, nephron numbers in neonates and in adults have been shown to be related positively to birth weight across the range of birth weights (99; 100). Other suggested mechanisms in the development of hypertension include the renin-angiotensin system which plays a role in both nephrogenesis and the development of

hypertension (81; 101), altered growth hormone secretion (102) and changes in vascular structure or function (103-106).

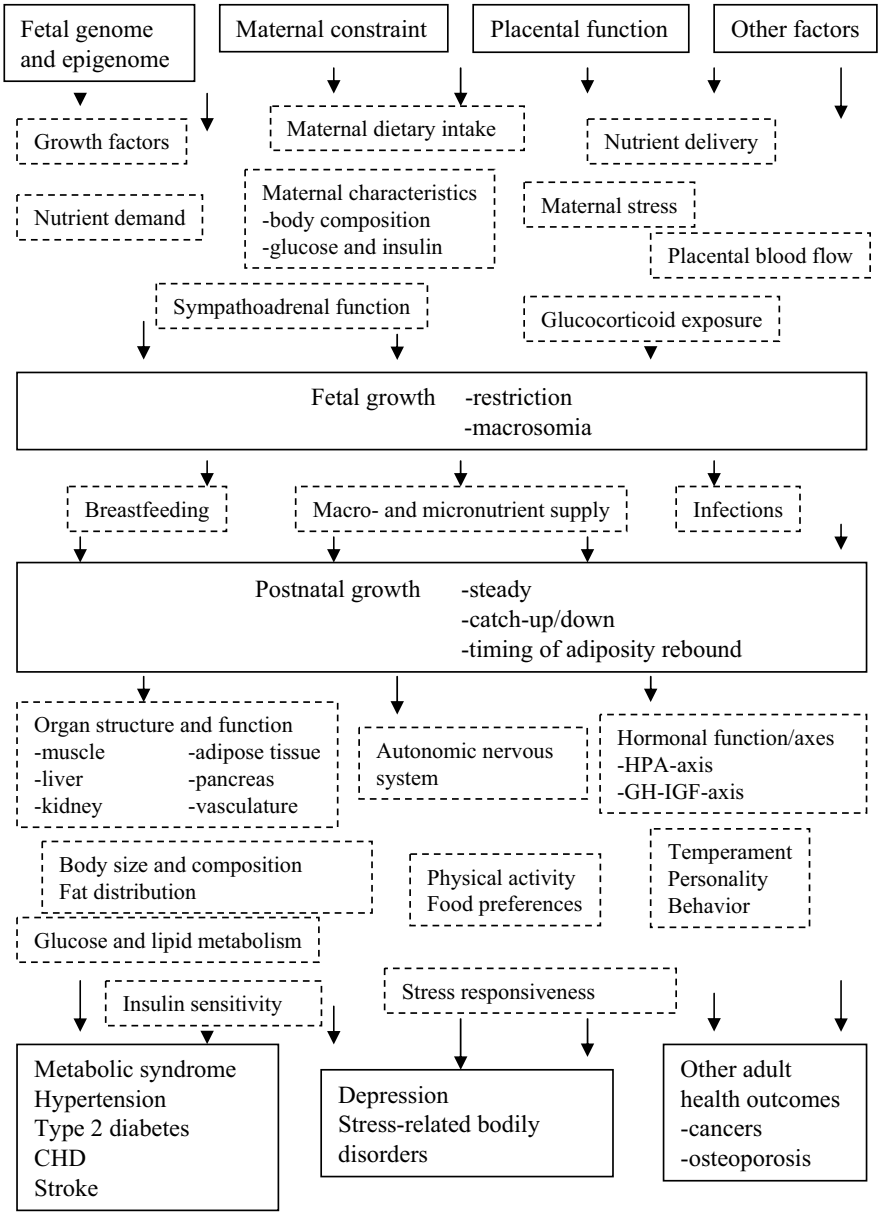

Figure 3. The concept of developmental origin of adult health and disease: potential internal and external mechanisms operating during the growth period. These mechanisms describe how the adversities during critical periods of early life are retained into adult life and translated into diseases. Modified from Räikkönen et al 2008 (82).

Programming may also include changes in body composition such as reduced muscle mass and altered muscle function (107-110). Small birth size for gestational age, the indicator of fetal adaptations, seems to be primarily attributable to reduced lean body mass (111) and this deficit tracks through childhood (112) and adolescence (113) into adulthood (114-117). Catch-up growth after fetal or infancy gowth retardation has been suggested to favour fat accumulation, specifically abdominal fat, at the cost of lean mass, and this tendency may persist into adulthood (60; 118-120). These changes in body composition may play a role in the development of insulin resistance which is the major metabolic disturbance behind the metabolic syndrome and related traits; actually the dynamic phase of catch-up growth has also been presented as a state of insulin resistance (121). Other suggested mechanisms include epigenetic modification of genes such as changes in expression of imprinted genes that regulate placental nutrient transfer capacity (122) and altered hormone sensitivity (123).

2.4 Developmental origin of components of the metabolic syndrome

2.4.1 Early growth and the adult metabolic syndrome

The metabolic syndrome is a clustering of risk factors for cardiovascular diseases and type 2 diabetes. The definition of this syndrome varies, but the central features are abdominal obesity and insulin resistance (3; 124; 125). Which comes first and whether there is a single underlying pathogenetic mechanism is still under debate. Other metabolic abnormalities include varying degrees of glucose intolerance, dyslipidaemia and hypertension. Table 1 presents the current definition in Europid subjects by the International Diabetes Federation (2; 3).

Studies on developmental origins of adult disease have strongly linked small birth size or early growth with the individual components of the metabolic syndrome and related diseases (5; 16; 126-129). Studies using an accepted definition of the metabolic syndrome rather than its components have been less consistent in linking small birth size with the syndrome. Obviously the different definitions in these studies partly explain this. Middle-aged Finnish men in the lowest third of birth weight or ponderal index were roughly two times more likely to have the metabolic syndrome than men in the highest tertile (130). The risk related to low birth weight was comparable to that in young adults in Netherlands (131). In contrast, in another Dutch study the prevalence of the metabolic syndrome was not greater after prenatal exposure to famine, nor was it associated with a reduced birth weight in that study

(132), in young adults in Amsterdam (133) or in middle-aged men and women in Newcastle (134).

Table 1. Definition of the metabolic syndrome by the International Diabetes Federation 2005 (2; 3).

Central obesity
Waist circumference (values are ethnicity specific)
≥ 94 cm in Europid men
≥ 80 cm in Europid women
Plus any two:
Raised triglyceride level
≥ 1.7 mmol/l
or specific treatment for this lipid abnormality
Reduced HDL cholesterol
<1.03 mmol/l in men
<1.29 mmol/l in women
or specific treatment for this lipid abnormality
Raised blood pressure
systolic ≥ 130 mmHg
diastolic ≥ 85 mmHg
or treatment of previously diagnosed hypertension
Raised fasting plasma glucose
≥ 5.6 mmol/l
or previously diagnosed type 2 diabetes

Studies assessing the relationship between childhood obesity or growth and adult metabolic syndrome are difficult to compare because of their different approaches with various ages at which the children or adults were assessed and various definitions of obesity, mostly based on body mass index (BMI). The limitations of BMI as an index of obesity must also be recognized since it denotes both lean and fat mass. In a study with cross-sectional data on both childhood and adulthood, children with their BMI in the highest quartile at the age of 7 years had an increased risk of the metabolic syndrome at the age of 36-46 years (135). However, in another study the sensitivity of childhood obesity in predicting the adult metabolic syndrome was low, with 37% for the 85th and 15% for the 95th childhood BMI percentile as the cut-off value, and only half of the obese children had the metabolic syndrome as adults (136). To improve the precision to identify children who eventually develop metabolic complications, other markers in addition to obesity should be included in possible screening programs.

A few studies have assessed the persistence or change in relative size between two points in time in relation to the presence of the adult metabolic syndrome. Catch-up growth between birth and adulthood in men was predictive of the syndrome in two studies (134; 137). An upward shift in age-specific BMI percentile from childhood to adulthood increased the risk of the metabolic syndrome considerably (138). The role of the timing of the shift was not assessed although the study included children with a wide age range (5-19 years with a mean of 12.8 years). However, in another study childhood obesity by the age of 7 years, that tracked into adulthood, was a greater risk factor for the metabolic syndrome than obesity that developed during later life (139). In contrast, in a study assessing the various cardiometabolic risk factor levels of the metabolic syndrome, rather than the presence of a clinic entity, these risk factor levels in obese subjects did not vary by the age of obesity onset (≤8 years, 12-17 years, ≥18 years) (140). The relationship between childhood obesity and the risk factor levels resulted from the persistence of the obesity status from childhood to adulthood (140).

Timing of the increase or decrease in growth rate as evidenced by centile crossing, irrespective of the absolute level of fatness, may be critical for whether the change is deleterious or beneficial for later health. This is exemplified by several studies. The age of obesity onset has been suggested to be crucial for later obesity, its persistence and metabolic complications (141; 142); patterns of childhood growth that are related to adult obesity may differ from those related to the development of metabolic adversities (143); the hypothesis that metabolically healthy obese subjects differ from obese subjects with the metabolic syndrome in terms of childhood growth rate changes and their timing receives some support from one study on children (144). Thus the need for longitudinal studies with data on BMI or preferably more specific measurements of adiposity at several points during childhood is obvious.

A recent study illustrated how different adult outcomes were preceded by different pathways of growth. When adults with and without the metabolic syndrome were compared, the onset of a difference in BMI was shown to occur at age 8 years in boys and 13 years in girls whereas the growth curves diverged at ages 3 years in boys and 9 years in girls in those who did and did not become obese (BMI≥30) (Sun 2008). Remarkably, despite the difference, the BMI values of most children at risk of metabolic adversities later in life did not exceed the recommended arbitrary percentile thresholds for overweight.

2.4.2 Birth size and blood pressure level

The inverse relationship between weight at birth and systolic blood pressure (BP) level has been extensively studied across several ethnic groups and in age groups ranging from infancy to old age. These studies have been reviewed by Law et al. (145) and Huxley et al. (146), summarizing data from 28 to 80 studies with 15000 to 444000 subjects, respectively. Table 2 presents data on studies of the relationship between birth weight and systolic BP in subjects aged 50 years or more. In general, the first two reviews estimated that a 1 kg higher birth weight is associated with a 2 mmHg lower systolic BP.

This conclusion, however, was challenged by a third review by Huxley et al. claiming that the inverse association between birth weight and current BP may chiefly reflect the impact of random error, reporting bias, and the inappropriate adjustment for potential confounders such as current weight (11); the latter may reflect the importance of postnatal growth (41). The proposal of a statistical artefact was supported by Tu et al. with their simplified approach which showed that if both birth weight and adult BP are positively correlated with current weight while not correlated with each other, then adjustment for current weight can induce a negative correlation between birth weight and adult BP (147). Studies and commentaries thereafter have addressed these questions. Publication bias has been estimated to reduce the magnitude of the inverse association between birth weight and systolic BP but not to explain it (148). The suggestion by Huxley et al. that larger studies reporting weaker associations are more reliable has been criticized because these studies have included self-report of recalled blood pressure and subjects on antihypertensive drug therapy (149), the number of whom is higher by lower birth weight (150; 151). A study with comprehensive follow-up data from early pregnancy up to early thirties was able to take into account a large scale of potential confounders including current size; the inverse association was found whether or not adjusted for current BMI (152). That study and others have emphasized the role of gestational age (152; 153).

To overcome the limitations of previous reviews, the most recent meta-analysis used a standardized meta-regression method on both published and unpublished raw data from 20 cohort studies in six Nordic countries including data from the Helsinki Birth Cohort Study (50). That study showed, again, an inverse association between birth weight and systolic BP. As expected, it was strengthened after adjustment for current BMI, and attenuated but still significant after adjustment for gestational age. There was an apparent sex-difference: the association was linear among males but in females only up to the birth weight of 4 kg after which it was inverted. Non-linearity of the association has also been described in a study on five European cohorts (153).

Table 2. Studies of the relationship between birth weight and systolic blood pressure (SBP) in subjects aged 50 years or more. Modified from Huxley et al. 2000 (146), Stein et al. 2006 (83) and Hardy et al. 2005 (153).

Authors	Place	Sex	n	Year of birth	Age (years)	Mean SBP	Regression of SBP on birth weight (mmHg/kg) (95% CI)
Roseboom et al.	Netherlands	Mixed	739	1943-1947	50	125.5	-2.7 (-5.1 to -0.3)[b]
Curhan et al	USA	F	71000	Not given	58	126.1	-1.39 (-1.49 to -1.26)[c]
Yarbrough et al.	California, USA	F	303	Not given	50-84	134.4	1.41 (p>0.10)[b]
Leon et al.	Uppsala, Sweden	M	1333	1920-1924	50	133	-2.2 (-4.2 to -0.3)[d]
Martyn et al	Sheffield, UK	Mixed	336	1939-1941	51-54	Not given	-5.9 (-10.1 to -1.8)[e]
Law et al.	Preston, UK	M	117	1935-1938	59-63	154	-3.4 (-9.1 to 2.3)[a]
	Preston, UK	F	103	1935-1938	59-63	149	-3.4 (-13.6 to 6.8)[a]
Law et al.	Hertfordshire, UK	M	426	1920-1930	64-71	162	-3 (-6.9 to 0.9)[a]
	Hertfordshire, UK	F	203	1923-1930	64-71	159	-2.7 (-8.8 to 3.4)[a]
Law et al.	Hertfordshire, UK	M	418	1920-1930		166	-4.9 (-8.8 to -1)[a]
	Hertfordshire, UK	F	184	1923-1930		161	-5.5 (-12.2 to 1.2)[a]
Stein et al.	Netherlands	mixed	657	1943-1947	59 (mean)	140.3	-4.14 (-7.24 to -1.03)[f]
Hardy et al.	Faroe Islands	M	204	1927/37	52-62	142	-0.2 (-5.1 to 4.6)[f]
	UK	M	1146	1946	53	141	-2.6 (-4.8 to -0.3)[f]
	UK	F	1146	1946	53	132	-2.4 (-4.8 to -0.1)[f]

[a] adjusted for current weight; [b] adjusted for age, sex and current weight; [c] adjusted for sex, current weight and parental blood pressures; [d] adjusted for age and current weight; [e] adjusted for sex, current weight, alcohol consumption, gestational age; [f] unadjusted

The magnitude of the association in the Nordic study was estimated to be -0.75 mmHg/kg in men aged 18-24 years with a change of -0.26 mmHg/kg for each 10-year increase in age. The corresponding estimates for women with a birth weight below 4 kg were -1.74 (reference age 25-34 years) and -0.53 mmHg/kg. Calculated from these, in men and women aged over 64 years the regression coefficients would be -2.05 and -3.86, respectively. This amplification over the lifecourse has previously been proposed by Law et al. (154) but it could not be confirmed in a longitudinal study with repeated measurements in middle age (155). There may be a cohort effect or a wider distribution of systolic BP in the older populations (50; 153); nevertheless, the effects of age and year of birth are difficult to disentangle (50).

While the association between birth weight and systolic BP level has been shown to be robust, the small effect of birth weight on BP seems to contradict with the substantial effect on the prevalence of hypertension (150). The mechanisms for this and several other aspects deserve attention. Only two other studies have compared the associations of birth weight with systolic BP between hypertensive and non-hypertensive subjects (155; 156). Studies of a possible common genetic factor behind both fetal growth and later risk for high BP or the effects of antihypertensive medication are rare (157). Moreover, most studies have based the evaluations of the association on an office BP measurement in a single occasion. Discussion on statistical issues continues to highlight the complexity of research on developmental origins of adult health (158; 159).

PPAR γ2 gene polymorphism

Developmental plasticity may be modified by genes. Environmental factors may produce different outcomes depending on the genes of the individual. Certain genotypes may be protective whereas other genotypes may make an individual more vulnerable to adverse early experiences. Since insulin resistance is closely related to many diseases linked to poor early growth, polymorphisms of genes involved in glucose metabolism and adipogenesis are obvious candidates for studies on the interactions between genes and early environment.

The peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear hormone receptor that has a crucial role in regulation of target genes involved in adipogenesis, lipid and glucose metabolism (160; 161). PPARγ can bind a variety of endogenic compounds and is the main target of the insulin-sensitizing drugs, thiazolidinediones, which are used in the treatment of type 2 diabetes. The isoform PPARγ2 is expressed predominantly in adipose tissue. The most prevalent known variant of the PPARγ2-gene is Pro12Ala polymorphism, in which alanine substitutes proline (C-toG nucleotide change) in codon 12 in the PPARγ2-specific exon B, resulting in partial loss of function (162; 163). Among Caucasian population the allelic

frequency of the Ala variant is approximately 0.12, indicating a carrier prevalence of the polymorphism in this ethnic group of approximately 25% (162; 163). In our study population the frequency of Ala-allele was 0.173 (164).

Two meta-analyses have confirmed that the Ala-allele is associated with a significantly reduced individual and population-attributable risk for type 2 diabetes (165; 166). In this respect the PPARγ gene is one of the most important genes identified to date at the population level: if everybody carried the Ala-allele, according to the most optimistic estimate, the global prevalence of type 2 diabetes would be 25% lower (166). The risk-reduction is probably mediated mainly by greater insulin sensitivity (160; 163; 167), in which the adipose tissue has an active role (160; 167).

However, the environment may considerably modify the effects of the Pro12Ala polymorphism on insulin resistance which may partly explain the inconsistencies in different studies. A meta-analysis in nondiabetic subjects found that only in the obese subgroup (BMI $\geq$ 30 kg/m^2) the surrogate markers of insulin resistance were significantly higher in the Pro12Pro carriers (168). Obesity and ethnic background interact with the polymorphism also on the prevalence of type 2 diabetes (169). Other evidence on interactions affecting insulin sensitivity in relation to Pro12Ala polymorphism include studies on the effects of other genes (170-172), nutrients (173), exercise (173) and development *in utero* (164; 174). Overall, it has been suggested that the carriers of the Ala-allele are protected against adverse environmental influences, such as a high-fat diet and a lack of exercise, and thus are less prone to develop diabetes and cardiovascular disease (175).

Since insulin resistance is closely linked not only with type 2 diabetes but also with hypertension, it is not surprising that Pro12Ala polymorphism has also been studied in association with blood pressure and hypertension. These studies show even more variation. In Caucasian subjects the Ala-allele has been found to be associated with higher systolic and diastolic BP in family members of type 2 diabetic subjects (176), with lower diastolic BP in diabetic men (177) and higher diastolic BP in obese diabetic subjects (178), or no relationship has been found between polymorphism and systolic or diastolic BP levels or hypertension in nondiabetic or diabetic subjects (179; 180). However, subjects with Pro12Pro genotype and normal plasma homocysteine values have had a higher risk for hypertension (181). Taken together, similarly as with insulin resistance, environmental factors are likely to modify the effects of Pro12Ala polymorphism on blood pressure. There have been no studies on what kind of role early growth might play in this respect.

2.4.3 Birth size, glucose intolerance and physical activity

While several studies have suggested an inverse linear relationship between birth weight and the risk of type 2 diabetes (5; 19; 20; 127), a recent meta-analysis showed that it is U-shaped, high birth weight being associated with increased risk of type 2 diabetes to a similar extent as low birth weight (182). Fetal macrosomia, resulting from exposure to high glucose levels because of maternal diabetes, may contribute to this association since the offsping of diabetic mothers have been shown to have an increased risk of type 2 diabetes in later life (183). The higher end of the birth weight distribution may thus become more important in predicting the disease risk in industrialized countries with high prevalence of overweight women who have an increased risk of maternal diabetes.

Physical exercise has a favourable effect on several cardiometabolic risk factors: it decreases blood glucose levels, improves insulin sensitivity and serum lipid profiles, decreases body fat mass and reduces blood pressure level (184). Therefore, it is not surprising that the risk of type 2 diabetes can be reduced by lifestyle intervention including increasing physical activity (185). Those subjects had an increased risk for type 2 diabetes because of their impaired glucose tolerance status. It remains to be shown whether subjects with another risk factor, small birth size, might as well be protected from the development of type 2 diabetes by physical activity. Furthermore, physical fitness or activity in itself may be related to birth size (130; 186), possibly because of changes in e.g. cardiopulmonary or muscle capacity (1).

2.4.4 Birth size, early growth and adult body composition

Human body composition can be presented at several levels ranging from chemical elements to molecular, cellular and tissue level. A two-compartment model that divides the body into fat and fat-free masses is classically used in studies on physical fitness, nutritional status and obesity. The term lean mass is often used synonymously to fat-free mass.

Estimates of total body fat and lean mass can be assessed by a variety of methods. These include anthropometry, such as measuring the thickness of subcutaneous fat by calipers in multiple regions of the body, underwater weighing which is based on different buoyancy of body fat and lean tissue, scanning of the body by dual energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT), and bioelectric impedance analysis which is presented below. All these methods have their strengths and limitations. For example, the most accurate methods, MRI and CT,

are expensive and not easily available, and the latter exposes the subject to a considerable level of X-rays especially in repeated examinations.

The largest constituent of fat-free mass is water. Because only water in the body conducts electrical current, the resistance of an electrical current through the body can be used to estimate total body water and thus fat-free mass. This is called bioimpedance analysis. Early analyzers could not distinguish intracellular water from extracellular water and the measurement was restricted to, for example, the upper body. Technological improvements, such as the use of a spectrum of electrical flows and 4 pairs of electrodes to measure the resistance of each limb and trunk separately, have improved the accuracy of this method (187).

Adult obesity and low birth weight are both risk factors for the metabolic syndrome. Paradoxically, adult obesity is predicted by high birth weight (143; 188-192). However, since obesity has mostly been assessed by BMI which denotes lean mass as well as fat mass, methods that distinguish these components may illuminate this paradox. Another reason to analyze body composition in relation to early growth is the evidence of certain growth patterns as predictors of adult cardiovascular disease and type 2 diabetes or their risk factors (64; 65; 71; 129; 193); effects of early growth on body composition may play a role in the development of these diseases. Insulin resistance, the central component of the metabolic syndrome, is in itself linked to low birth weight or thinness at birth (19; 75; 194-196). This association is amplified in subjects whose small size or thinness at birth were followed by later catch-up growth in BMI, even in the absence of actual overweight or development of obesity (19; 171; 197-201).

Studies on body composition have shown that infants born small for gestational age seem to have reduced lean mass, rather than fat mass, throughout childhood and adulthood (111-117). Since the main component of lean mass, muscle mass, is important for glucose homeostasis regulation, the relative deficiency of lean mass may predispose to insulin resistance.

Fat distribution pattern has been suggested to be programmed during fetal life (202-205). While these results seem to support the fetal origin of the metabolic syndrome, with a large waist circumference as a key feature, many of these studies have assessed abdominal obesity by the waist-hip ratio. The relationship of low birth weight with higher waist-hip ratio has been suggested to represent a reduced hip size rather than abdominal deposition of fat (204). Furthermore, anthropometric measurements do not distinguish subcutaneous and intra-abdominal fat, the latter of which is the metabolically active component.

Studies with an accurate method to measure abdominal fat are rare (206-208). In a twin study utilising magnetic resonance imaging birth weight was inversely

associated with abdominal visceral and subcutaneous fat (207). One study suggests an early interplay between insulin resistance and abdominal fat deposition (208). In that study children born small for gestational age, compared with children born appropriate for gestational age, shifted from insulin sensitivity to insulin resistance between ages 2 and 4 years after largely completed catch-up growth by 2 years of age, and the development of insulin resistance was accompanied by increased gain of fat and deposition of fat more centrally according to a DXA scan despite similar gain in BMI.

Few studies with various methods have assessed the effects of childhood growth on body components in later life. A study in 9 year old boys showed that rapid weight gain in infancy was associated with height or lean mass whereas weight gain between 1 and 4 years of age predicted both lean mass and fatness, and rapid weight gain thereafter only fatness (209). Another study on 4 year old children showed that at age 2 years body composition of children born small for gestational age, despite largely completed catch-up growth, did not differ from that of children born appropriate for gestational age (208). In contrast, between ages 2 and 4 years they gained more fat, specifically abdominal fat, and less lean mass while changes in overall weight, height and BMI were similar. In Guatemalan young adults accelerated increase in height between birth and 2 years of age was related to higher fat percentage (210). Three studies in adults have suggested that high rates of weight or BMI gain in infancy and childhood are associated with an increase in both adult lean mass and adiposity (211-213). However, in the young Indian adults the gain in BMI up to 8 years of age was more strongly associated with adult lean mass than with adiposity while the strength of the association with adult adiposity increased steeply between 2 and 8 years and was sustained up to 14 years of age (212).

3 AIMS OF THE STUDY

The overall aim was to explore the associations of early growth with components of the adult metabolic syndrome. Another focus was on factors that may underlie or modify these associations: a well-characterized gene polymorphism, physical activity and adult body composition, all of which are known to affect insulin sensitivity.

The specific objectives were:

1. To assess the effects of birth size on blood pressure levels in men and women with and without established hypertension at 65-75 years of age (Study I).
2. To assess whether peroxisome proliferator-activated receptor γ 2 (PPARγ2) gene polymorphism interacts with the relationship between birth size and adult blood pressure level or with the relationship between birth size and the use of any class of antihypertensive medication in hypertensive 65-75 year old men and women (Study II).
3. To examine whether habitual regular exercise has a protective effect against glucose intolerance in 65-75 year old subjects with a recognized risk factor for glucose intolerance, i.e. small body size at birth (Study III).
4. To examine how body size at birth is related to adult body composition at 56-70 years of age, and how this is related to grip strength (Study IV).
5. To examine how change in body mass index throughout childhood is related to adult lean and fat mass at 56-70 years of age (Study V).

4 SUBJECTS AND METHODS

4.1 Study populations

Participants of these studies belong to clinically examined subsets of two birth cohorts with data on size at birth and during childhood. These original cohorts comprise 7086 and 8760 subjects. They were born as singletons in 1924-33 and 1934-44 in the Helsinki University Central Hospital, went to school in Helsinki and were alive and residing in Finland in the year 1971. Members of the younger cohort attended child welfare clinics. Of the older cohort, 500 subjects participated in a clinical study at the age of 65 to 75 years between December 1998 and March 2000. Of the younger cohort, 2003 subjects participated in the clinical study at the age of 56 to 70 years between August 2001 and March 2004.

Data on the cohorts has been collected from three types of records preserved in hospital archives or in the Helsinki City Archives. First, standardised birth records include birth weight (rounded to the nearest 10 g) and length (to the nearest 0.5 cm), father's occupation, and mother's age, height, weight (recorded before delivery), parity and date of her last menstrual period. Second, school health records on children who attended the schools in Helsinki include serial height and weight measurements recorded from 7 to 15 years of age. Third, child welfare records with data on weight and height in infancy and at intervals thereafter are available for the younger cohort. On average, men and women from the clinically examined subset of the younger cohort have a median of 10 measurements of weight and height between birth and the age of 2 years and 8 measurements between 2 and 11 years.

Each individual, identified by linking these records, was matched with the population register in order to find the personal identification number which has been allocated to each member of the Finnish population since 1971. This unique number was then used to trace the cohort members who were still alive and living in Finland. Members of the older cohort (n=5210) were sent a postal questionnaire in the year 1998 and members of the younger cohort (n=10530) in the year 2001. Participants of the clinical studies were selected among those who responded and gave us permission to take further contacts.

Studies I-III. A total of 674 people from the older cohort still living in the Helsinki area were invited to attend a clinical study and 500 of them agreed to do so. Characteristics and variables of interest of these subjects are presented in Table 3. Of them, only subjects with medication for hypertension were included in Study II.

Studies IV-V. To obtain a sample size in excess of 2000 people, 2902 randomly selected people from the younger cohort were invited to attend a clinical study. Of them, 2003 participated and were included in Study IV. 1917 men and women had data on their body composition and were included in Study V. Characteristics of the participants are presented in Table 4.

4.2 Clinical examination

Subjects attended the clinic in the morning between 8.00 and 10.00, after an overnight fast, to have blood tests. Body weight was measured to the nearest 0.1 kg in light clothing without shoes, and height was measured to the nearest millimetre. Body mass index was calculated as kg/m^2. Waist circumference was measured with a soft tape midway between the lowest ribs and the iliac crest and that of hip at the level of great trochanters.

The Ethics Committee of the National Public Health Institute had approved the study protocol of studies I-III. Studies IV-V were approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from each participant.

Studies I-III (older cohort). Blood pressure was measured after a 10-min rest from the right arm in the sitting position using a standard mercury sphygmomanometer (Omron Matsutaka Europe, Hoofdorp, the Netherlands) and the mean of two successive readings was recorded. Subjects on medication for hypertension were asked not to take their medication on the morning of clinic attendance.

A 24-hour ambulatory blood pressure monitoring with a portable device (SpaceLabs Medical 90207, SpaceLabs Inc, Redmond, Washington) was performed on a subsample of 169 subjects. Because of lack of sufficient equipment to offer ambulatory monitoring to all subjects, we invited subjects to participate as equipment became available. Those currently on drug therapy resumed it before monitoring commenced. The recorder was attached before midday to the non-dominant arm. Blood pressure was measured at 20-minute intervals from 6:00 AM to 9.00 PM and at 60-minute intervals from 9:00 PM to 6:00 AM. The ambulatory pressure was averaged over 24 hours.

In Study I subjects were defined as hypertensive if they reported that they had been previously diagnosed by a physician as having hypertension. 175/213 (82%) of them were currently on antihypertensive medication. In Study II, definition of hypertension was based on the use of antihypertensive medication (Table 1). Medication was divided into four classes: diuretics, beta-adrenergic

receptor blockers, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers (ACEI/ARB) and calcium channel antagonists.

Percentage body fat was determined by a handheld bioelectric impedance analyser (Omron Body Logic Body Fat Analyzer; Omron Healthcare).

Data on exercise habits were derived from self-administered questionnaires. Frequent exercise was defined as 3 or more times of regular leisure time exercise per week. Intensity of exercise was grouped into two categories: 1. light (such as walking) or 2. moderate (such as brisk walking) or strenuous (such as jogging). Yearly energy expenditure (kcal) on physical activity was estimated by a validated exercise questionnaire (KIHD 12-month leisure time physical acitivity history, (214)). In the exercise history, the subjects were asked to report the frequency, average duration and intensity class of each leisure time physical activity during the previous 12 months. An exercise-related yearly energy expenditure score (kcal) was then calculated by multiplying the duration of each activity by the caloric coefficient of the specific activity and intensity class.

An oral glucose tolerance test (OGTT) was started in the morning, after an overnight fast, with the ingestion of 75 g of glucose. Plasma glucose concentrations were measured by a hexokinase method from samples drawn at 0, 30 and 120 min. The results were interpreted according to the WHO 1999 criteria (215). Insulin concentrations were determined by a two-site immunoradiometric assay. The homeostatic model assessment index of basal insulin resistance was calculated as the product of fasting glucose and insulin (mU/l) divided by 22.5.

The Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 (PPARγ2) gene was determined for 476 of the 500 subjects by the polymerase chain reaction single-strand conformation polymorphism method. The genotypes were encoded as 0 = Pro12Pro and 1 = Pro12Ala and Ala12Ala.

Table 3. Characteristics of the 65 to 75 year old participants and selected variables of interest in Studies I-III. Mean value (SD) unless otherwise stated.

Birth and adult characteristics				
	Men, n=186		Women, n=314	
Birth weight, g	3445 (458)		3296 (464)	
Length at birth, cm	50.2 (1.7)		49.7 (1.8)	
Ponderal index, kg/m^3	27.1 (2.4)		26.7 (2.3)	
Age at clinical examination, years	69.4 (2.9)		69.7 (2.7)	
Adult body mass index, kg/m^2	27.3 (3.9)		27.8 (4.6)	
	Study I			
	Inclusion criteria: Attendance to the clinical study, n=500			
	Normotensive (57%)		Hypertensive (43%)	
	Men, n=111	Women, n=176	Men, n=75	Women, n=138
Adult body size				
Height, cm	174.4 ((5.5)	160.5 (5.1)	174.4 (5.9)	160.2 (6.1)
Waist circumference, cm	99.6 (10.0)	88.5 (10.8)**	102.5 (11.4)	93.4 (11.7)**
Body fat, %	30.0 % (4.3)	40.4 (4.7)	30.8 (4.4)	41.7 (4.2)
Blood pressures, mmHg				
Clinic systolic	151 (20)**	154 (22)**	168 (21)**	166 (20)**
Clinic diastolic	87 (11)**	85 (9)**	96 (10)**	91 (10)**
24-hour ambulatory systolic[a]	130 (14)*	129 (13)*	138 (17)*	135 (14)*
24-hour ambulatory diastolic[a]	77 (9)*	74 (7)	82 (8)*	76 (8)
	Study II			
	Inclusion criteria: Use of antihypertensive medication n=208			
PPAR-γ2 gene polymorphism[b]	Pro12Pro, n=141		Pro12Ala/Ala12Ala, n=67	
Blood pressures, mmHg				
Clinic systolic	165 (21)		166 (21)	
Clinic diastolic	91 (11)		91 (10)	
24-hour ambulatory systolic[a]	135 (14)		132 (18)	
24-hour ambulatory diastolic[a]	77 (9)		76 (8)	
Fasting plasma insulin, pmol/l[c]	86 (1.3)**		63 (1.8)**	
HOMA index[d]	3.3 (2.0)**		2.3 (2.0)**	
Antihypertensive drugs, n (%)[e]				
Diuretics		68 (33%)		
β-adrenergic receptor blockers		119 (57%)		
ACEI/ARB [f]		64 (31%)		
Calcium channel antagonists		57 (27%)		
	Study III			
	Inclusion criteria: Attendance to the clinical study, n=500			
Glucose tolerance status, n (%)				
Normal glucose tolerance		257 (51%)		
Impaired glucose tolerance		141 (28%)		
Diabetes		102 (20%)		
Frequency of exercise, n (%)				
<3 times per week		268 (54%)		
≥3 times per week		217 (43%)		
Intensity of exercise, n (%)				
Light		262 (52%)		
Moderate[g] or strenuous		233 (47%)		

*p<0.05; **p < 0.001 in Study I for difference between normotensive and hypertensive subjects; in Study II for difference between different PPAR-γ2 gene polymorphism carriers.

[a] Performed on a subsample of 169 (72 hypertensive) subjects. [b] Peroxisome proliferator-activated receptor-γ2. [c] Geometric means. [d] Homeostatic model assessment insulin resistance index. [e] 82 subjects received more than one medication. [f] Angiotensin converting enzyme inhibitors and angiotensin-receptor blockers. [g] Comparable to brisk walking.

Studies IV-V (younger cohort). Estimates of total lean and fat mass were measured by a bioelectrical impedance analysis (BIA) using the InBody 3.0 eight-polar tactile electrode system (Biospace Co., Ltd, Seoul, Korea). This method was chosen because of its practicality in large epidemiological studies with limited time for examination of each subject (216; 217). The outputs of the analyser are based on segmental multifrequency analysis of each limb and trunk, and on measured values only. Empirical data, such as sex and age or population-specific algorithms, are not used (216-218). The method has been shown to have a reasonable accuracy in several ethnic groups including Europid men and women with a wide age range (219). Resistance was measured at frequencies of 5, 50, 250 and 500 kHz with the subject standing barefoot in light clothing on four foot electrodes on the platform of the analyser and gripping the two palm and thumb electrodes. The estimates of body components were derived from calculations using the manufacturer's software.

Isometric grip strength of the dominating hand was tested by a Newtest Grip Force dynamometer (Newtest Oy, Oulu, Finland). The maximum value of three squeezes was used in analyses. The dynamometer was not available, or the test was not performed due to hand pain, for 104 subjects.

Smoking habits and frequency of leisure-time exercise were derived from self-administered questionnaires. A subject was defined as a smoker if he/she smoked one or more cigarettes per day, and as physically active if he/she exercised regularly and at least moderately three or more times per day. Moderate exercise was defined as comparable to brisk walking. Occupation-based social class was derived from the census data in 1980. Social class in childhood (upper middle, lower middle or manual worker) was based on the father's occupation recorded in birth, child welfare clinic and school records, of which the occupation indicating the highest social class was chosen for the analyses.

Table 4a. Childhood characteristics of the 56 to 70 year old men and women in Studies IV-V. Mean value (SD) unless otherwise stated.

	Study IV (n=2003)		**Study V** (n=1917)*	
Characteristics at birth and in childhood	Men (n=928)	Women (n=1075)	Men (n=885)	Women (n=1032)
Weight				
Birth, g	3476 (501)	3353 (465)	3472 (502)	3349 (465)
1 year, kg			10.5 (1.0)	9.9 (1.0)
2 years, kg			12.4 (1.1)	11.9 (1.1)
7 years, kg			22.6 (2.6	22.2 (2.9)
11 years, kg			33.9 (4.6)	34.4 (5.7)
Length/Height, cm				
Birth	50.7 (2.1)	50.0 (1.8)	50.7 (2.1)	50.0 (1.8)
1 year			76.6 (2.5)	74.9 (2.5)
2 years			86.8 (3.0)	85.5 (3.0)
7 years			121.0 (4.8)	120.0 (4.6)
11 years			141.7 (5.9)	141.6 (6.6)
BMI, kg/m^2				
Birth			13.5 (1.2)	13.4 (1.2)
1 year			17.8 (1.3)	17.6 (1.4)
2 years			16.6 (1.2)	16.4 (1.2)
7 years			15.5 (1.1)	15.5 (1.3)
11 years			16.8 (1.5)	17.1 (1.9)
Ponderal index at birth, kg/m^3	26.6 (2.3)	26.7 (2.2)		
Gestational age, days	280 (11)	280 (11)	280 (11)	280 (11)
Maternal characteristics				
Age, years	28.8 (5.5)	28.7 (5.5)		
Height, cm	159.6 (6.0)	159.5 (5.6)		
Body mass index, kg/m^2	26.5 (3.0)	26.5 (2.8)		
Social class in childhood [a]				
Upper middle, %	19	15	19	15
Lower middle, %	24	22	24	22
Manual worker, %	57	63	57	63

*885 men and 1032 women with bioimpedance analysis. At least 832 observations in men and 976 in women were available for each variable.

[a] The highest social class indicated by father's occupation, derived from birth, child welfare clinic and school records.

Table 4b. Adult characteristics of the 56 to 70 year old men and women in Studies IV-V. Mean value (SD) unless otherwise stated.

Adult characteristics	**Study IV** (n=2003)		**Study V** (n=1917)*	
	Men (n=928)	Women (n=1075)	Men (n=885)	Women (n=1032)
Age, years	61.5 (2.8)	61.5 (3.0)	61.5 (2.8)	61.5 (3.0)
Height, cm	176.8 (6.0)	163.2 (5.7)	176.8 (6.0)	163.2 (5.7)
Weight, kg	86.2 (14.3)	73.8 (13.8)	86 (14)	74 (14)
BMI, kg/m^2	27.5 (4.2)	27.7 (5.0)	27.5 (4.0)	27.7 (5.0)
Waist circumference, cm	100.2 (1.1) [b]	90.2 (1.1) [b]	100.8 (11.3)	91.0 (12.9)
Hip circumference, cm	101.3 (1.1) [b]	103.9 (1.1) [b]		
Smokers, %	29	21	29	20
Physically active [c], %	46	44	46	44
Adult body composition				
Lean mass, kg	65.0 (7.9)	47.8 (5.7)	65.0 (7.8)	47.8 (5.7)
Lean mass index, kg/m^2			20.7 (1.8)	17.9 (1.7)
Fat mass, kg	19.6 (1.5)[b]	24.0 (1.5) [b]	20.9 (8.1)	25.7 (9.6)
Fat mass index, kg/m^2			6.7 (2.6)	9.7 (3.7)
Percent body fat	23.8 (6.0)	33.9 (6.9)	23.7 (5.9)	33.9 (6.9)
Adult muscle strength				
Grip strength, kg	40.2 (9.4)	22.9 (6.3)	40.4 (9.5)	22.8 (6.5)
Social class in adulthood [d]				
Higher official, %	40	25	40%	25%
Lower official, %	25	59	25%	59%
Manual worker, %	29	13	29%	12%
Self-employed, %	5	3	5%	3%

*885 men and 1032 women with bioimpedance analysis. At least 832 observations in men and 976 in women were available for each variable.
[b] Geometric means.
[c] Those exercising at al level comparable to brisk walking three or more times per week.
[d] Based on occupation, derived from the census data in 1980.

4.3 Statistical analyses

Studies I-III.. The blood pressure data was analysed by using multiple linear regression (p- values refer to continuous variables) and tabulation of means. In Study II, multiple logistic regression was used to analyze the proportion of subjects receiving antihypertensive medication and in Study III the relations between birth size, measures of exercise habits and glucose tolerance status. Variables that had skewed distributions (scores of yearly caloric expenditure on exercise, plasma glucose and insulin concentrations and homeostatic model assessment) were log-transformed for analyses.

Studies IV-V. All analyses were performed separately for each sex. One extremely obese man with a BMI of 68 kg/m^2 was excluded from the analyses.

In Study IV, linear regression with continuous variables was used to explore the relation of birth size with adult body size and composition and grip strength. Variables with skewed distribution (waist and hip circumference and fat mass) were log transformed to obtain a more symmetrical distribution. Three models were used: an unadjusted model, a model adjusted for age and adult height, and a model adjusted for age and adult BMI. To assess the effect of potential confounders we performed simultaneous regressions using as independent variables birth weight, adult height or BMI, and variables that in univariate analyses had been related to adult body composition. Subgroup analyses and tests of interaction were conducted to assess whether the effects of birth weight varied by adult body size and composition.

In Study V, each measurement of BMI in infancy and childhood for each individual was converted to a sex-specific z-score (SD score). The z-score is the number of standard deviations by which an observation differs from the mean for the whole study group. Because the children were not measured on their exact birthdays we obtained a z-score at each birthday by interpolation if measurements had been made within 2 years of that age. Piecewise linear interpolation was used on the z-scale to help accommodate non-linearity in raw BMI with age. The cross-sectional correlations between BMI z-scores in childhood and adult outcome variables were analyzed. Because the number of measurements was smaller at ages 3-5 years than at other ages (866-1318 versus 1833) and for consistency with previous studies on Helsinki birth cohort, data at birth and ages 1, 2, 7 and 11 years were chosen to be analyzed further. Periods between these ages are long enough to enable our aim to analyse the effects of a change from a growth path predicted by earlier growth.

Postnatal change in BMI between chosen ages was calculated by saving the residuals from linear regression models of BMI z-scores at each successive age versus BMI z-score at all earlier ages. These residuals, referred as conditional z-scores, are mutually uncorrelated, and enable the effects of change in BMI during different growth periods to be distinguished (220). The effects on adult body composition of BMI at birth and change in BMI after birth, during the four periods of growth, were examined by multivariate linear regression. Analyses were adjusted for age. Because body size indicates the absolute amounts of both lean and fat mass, in this study we used height-normalized indices as has been recommended (lean and fat mass were divided by height squared, LMI and FMI, respectively) (221; 222). Further adjustments with life style factors were performed. Significance was defined as $p < 0.05$. The statistical software used was SPSS for Windows (SPSS Inc., Chicago, USA).

5 RESULTS

5.1 Birth size, adult body size and blood pressure in 65-75 year old men and women with and without established hypertension

Birth and adult characteristics of the 500 study subjects are presented in Table 3. 43% of all subjects had hypertension diagnosed by a physician and 82% of them were currently on antihypertensive medication.

Size at birth and at the age of 65-75 years

The hypertensive subjects had shorter body length at birth (p=0.02) and lower placental weight (p=0.04) than those without hypertension. These associations were little changed by an adjustment for the duration of gestation (length, p=0.01; placental weight, p=0.04) or by the exclusion of people born before term.

Size at birth and adult blood pressure

Systolic BP was lower by greater birth weight and birth length. It was unrelated to the duration of gestation. These associations related to small body size at birth were confined to people with hypertension (Table 5, p=0.06 for interaction between birth weight and hypertension; p=0.05 for interaction between birth length and hypertension). Among people with hypertension a 1 kg increase in birth weight was associated with a 6.4 mmHg (95% CI, 1.0 to 11.9) decrease in systolic BP. The corresponding figure for nonhypertensive people was -1.2 (95% CI, -6.7 to 4.3), whereas for the total study sample it was 3.5 (95% CI, -0.6 to 7.6). Trends in men and women were similar. If hypertension was defined as systolic BP >160 mmHg, recorded at the clinic, rather than as a self-reported diagnosis, the findings were similar. This definition categorized 228 (46%) people as hypertensive. When we used lower values of systolic BP, 150 or 140 mmHg, the majority of the people were categorized as hypertensive. Nevertheless, the interaction between birth weight and hypertension remained. There were similar but not statistically significant trends with regard to diastolic BP.

Table 5. Systolic blood pressure recorded at the clinic in subjects with and without established hypertension according to birth weight and birth length. Values are mean (n).

Birth size	Nonhypertensive, mmHg	Hypertensive, mmHg	All
Birth weight, g			
2500	156 (10)	182 (15)	172
3000	150 (42)	164 (31)	156
3500	155 (139)	168 (98)	160
4000	152 (74)	164 (56)	157
>4000	152 (21)	163 (13)	156
p for trend*	0.63	0.02	0.10
Birth length, cm			
48	153 (37)	170 (42)	162
49	152 (60)	168 (36)	158
50	156 (87)	165 (66)	160
51	150 (55)	167 (42)	157
>51	152 (47)	164 (26)	156
p for trend*	0.67	0.01	0.03

*Adjusted for age, gender, and body mass index.

Table 6. Mean ambulatory 24-hour systolic blood pressure in subjects with and without established hypertension according to birth weight and birth length. Values are mean (n).

Birth size	Nonhypertensive, mmHg	Hypertensive, mmHg	All
Birth weight, g			
2500	127 (2)	145 (4)	139
3000	129 (16)	145 (12)	136
3500	130 (44)	134 (33)	131
4000	130 (25)	134 (20)	132
>4000	129 (9)	120 (2)	127
p for trend*	0.51	0.01	0.10
Birth length, cm			
48	126 (11)	143 (15)	136
49	130 (23)	137 (13)	133
50	132 (23)	135 (24)	133
51	129 (21)	132 (12)	130
>51	130 (18)	125 (6)	129
p for trend*	0.81	0.03	0.05

*Adjusted for age, gender, and body mass index.

The same associations were examined in the 169 people who had ambulatory BP measurements. The 24-hour mean BPs were 133/79 mmHg in men and 132/75 mmHg in women. The correlation between ambulatory measurements and those made at the clinic were 0.60 for systolic BP and 0.63 for diastolic pressure. Table 6 shows that the trends with systolic BP over 24 hours were similar to those for pressure recorded at the clinic (interaction between birth weight and hypertension, p=0.02; interaction between birth length and hypertension, p=0.07). Among people with hypertension a 1 kg increase in birth weight was associated with a 9.3 mmHg (95 CI, 2.1 to 16.5) decrease in systolic BP. The corresponding figure for nonhypertensive subjects was -1.9 (95% CI, -0.7 to 8.5), whereas for hypertensive and nonhypertensive subjects combined, it was 3.9 (95% CI, -0.7 to 8.5). There were no significant trends with diastolic pressure.

Table 7. Systolic blood pressure recorded at the clinic in subjects with and without established hypertension according to body mass index, waist circumference and body fat percentage. Values are mean (n).

Current body size	Nonhypertensive, mmHg	Hypertensive, mmHg	All
Body mass index, kg/m^2			
24	144 (63)	166 (32)	151
26	152 (68)	167 (39)	157
28	155 (53)	163 (46)	159
30	151 (45)	172 (32)	160
>30	164 (57)	168 (64)	166
p for trend*	<0.001	0.38	<0.001
Waist circumference			
80	147 (45)	167 (19)	153
90	148 (73)	165 (52)	155
100	153 (95)	168 (67)	159
110	158 (55)	168 (49)	163
>110	171 (18)	166 (26)	168
p for trend*	<0.001	0.66	<0.001
Body fat, %			
30	146 (58)	167 (34)	154
35	149 (60)	169 (38)	157
40	154 (69)	168 (42)	159
45	154 (71)	165 (61)	159
>45	168 (27)	165 (33)	167
p for trend*	<0.001	0.89	<0.001

*Adjusted for age and gender

Adult body size and blood pressure

High adult body mass index was associated with higher systolic BP. When we examined this trend separately among nonhypertensive and hypertensive subjects, we found that it was present only among nonhypertensive subjects. Table 7 shows that among people with hypertension systolic blood pressure was unrelated to body mass index, waist circumference, or percentage of body fat ($p<0.001$ for interaction between body mass index and hypertension). There were similar trends with regard to diastolic pressure ($p=0.01$ for interaction).

5.2 Birth size, PPARγ2 gene polymorphism and adult blood pressure in subjects on antihypertensive medication

Among the 208 men and women on antihypertensive medication, a 1 kg increase in birth weight was associated with a 6.9 mmHg (95% CI: 0.9-12.9) decrease in systolic BP and a 1 cm increase in birth length was associated with a 2.2 mmHg (95% CI: 0.7-3.7) decrease in systolic BP. Adjustment for duration of gestation had little effect.

The mean systolic BP varied according to the type of antihypertensive medication being used. It was 162 mmHg among people taking diuretics, 165 mmHg among those taking beta-blockers, 168 mmHg among those taking calcium channel-blocking agents, and 171 mmHg among those taking ACEI/ARBs. 82 subjects were taking more than one medication.

A total of 141 (68%) of the 208 subjects had the Pro12Pro polymorphism while 63 (30%) had the Pro12Ala and 4 (2%) had the Ala12Ala polymorphism of the PPARγ2 gene. Mean birth weight did not differ between the carriers of different polymorphisms.

Adult BP level according to birth size and PPARγ2 gene polymorphism

The greater the birth weight or length, the lower was the adult systolic BP measured at the clinic or during the ambulatory 24 h recording. Table 8 presents that this effect was confined to people with the Pro12Pro polymorphism, among whom a 1 kg increase in birth weight was associated with a 9.3 mmHg decrease (95% CI: 2.1-16.4, $p=0.01$) in clinic systolic BP and a 1 cm increase in birth length was associated with a 3.3 mmHg decrease (95% CI: 1.4-5.1, $p=0.001$) in clinic systolic BP. The interaction between the effects of birth length and the polymorphism was statistically significant ($p=0.05$). Exclusion of those subjects who had not reported a diagnosis of hypertension did not attenuate the associations. Findings in the two sexes were similar. There were no interactive effects on ambulatory or diastolic BP.

Birth size, PPARγ2 gene polymorphism and use of different types of antihypertensive medication

Low birth weight was related to the use of ACEI/ARB but not to the use of the other medications as presented in Table 9. This relationship remained significant when only those 126 subjects receiving monotherapy, 16 of them on ACEI/ARB, were included in analyses. In a simultaneous regression, use of ACEI/ARB was predicted by low birth weight ($p=0.04$), high systolic pressure ($p=0.02$), younger age ($p=0.02$) and by the use of anti-diabetic medication ($n=21$, $p=0.006$). The patient's PPARγ2 genotype, sex or BMI had no influence on the use of ACEI/ARB.

Table 10 presents the percentage of hypertensive people taking ACEI/ARB according to their birth weight and birth length and the PPARγ2 gene polymorphisms. In people with the Pro12Pro polymorphism, low birth weight and short body length at birth were both associated with the use of ACEI/ARB. This finding was detected also in those on monotherapy (15 of them on ACEI/ARB). These are statistically significant interactions between birth size and polymorphisms ($p=0.01$ for birth weight and $p=0.02$ for birth length).

Table 8. Mean clinic and 24-h ambulatory systolic and diastolic blood pressure (mmHg) in men and women with hypertension according to weight and length at birth and peroxisome proliferator-activated receptor-γ2 (PPARγ2) polymorphism. Number of subjects in parentheses.

	PPARγ2 polymorphism							
	Pro12Pro (n=141)				**Pro12Ala/Ala12Ala** (n=67)			
	Clinic SBP	Clinic DBP	24-h SBP	24-h DBP	Clinic SBP	Clinic DBP	24-h SBP	24-h DBP
Birth weight (g)								
≤3000	171 (28)	92 (28)	143 (12)	79 (12)	162 (14)	90 (14)	133 (5)	76 (5)
>3000	163 (113)	91 (113)	133 (39)	76 (12)	167 (53)	91 (53)	132 (18)	76 (18)
p-value	0.01	0.14	0.15	0.20	0.77	0.94	0.47	0.65
Adjusted p-value*	0.01	0.05	0.12	0.20	0.93	0.99	0.65	0.57
Length at birth (cm)								
≤49	170 (54)	92 (54)	140 (20)	79 (20)	163 (23)	91 (23)	129 (8)	73 (8)
>49	162 (87)	90 (87)	133 (31)	76 (31)	166 (43)	91 (43)	132 (14)	76 (14)
p-value	0.001	0.08	0.04	0.17	0.99	0.92	0.93	0.89
Adjusted p-value*	0.001	0.05	0.02	0.14	0.93	0.95	0.84	0.89
All	165 (141)	91 (141)	135 (51)	77 (51)	166 (67)	91 (67)	132 (23)	76 (23)

SBP, systolic blood pressure; DBP, diastolic blood pressure. p-values are for linear trends. *p-value adjusted for age, sex and body mass index.

Table 9. Percentage of men and women with hypertension receiving different antihypertensive medications according to birth weight. 82 subjects were taking more than 1 medication. Number of subjects in parentheses.

Birth weight (g)	**Diuretics**	**Beta-adrenergic receptor blockers**	**ACEI/ARB**	**Calcium channel antagonists**	**Hypertensive patients, n**
≤3000	31 (13)	55 (23)	48 (20)	29 (12)	42
>3000	33 (55)	58 (96)	27 (44)	27 (45)	166
All	33 (68)	57 (119)	31 (64)	27 (57)	208
p-value	0.97	0.80	0.03	0.60	
Adjusted p-value*	0.74	0.89	0.02	0.65	

ACEI/ARB, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. * p-value adjusted for age, sex and body mass index.

Table 10. Percentage of men and women with hypertension who were taking angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers according to peroxisome proliferator-activated receptor-γ2 (PPAR γ2) gene polymorphism and body size at birth.

	PPARγ2 polymorphism			
	Pro12Pro		**Pro12Ala/Ala12Ala**	
Characteristic	%	r/n	%	r/n
Birth weight (g)				
≤3000	64	18/28	14	2/14
>3000	26	29/113	28	15/53
All	33	47/141	25	17/67
p-value	0.003		0.32	
Adjusted p-value*	<0.001		0.25	
p-value for interaction	0.01			
Length at birth (cm)				
≤49	44	24/54	17	4/23
>49	26	23/87	28	12/43
All	33	47/141	24	16/66
p-value	0.01		0.18	
Adjusted p-value*	0.009		0.16	
p-value for interaction	0.02			

r/n are numbers of subjects taking angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and numbers of subjects with hypertension. One subject had unknown length at birth.

*p-value adjusted for age, sex and body mass index.

5.3 Birth size, regular physical activity and glucose intolerance

Table 3 presents the glucose tolerance status and exercise habits of the study subjects. 173 subjects scored their leisure time physical activity as moderate and 60 as strenuous; in most analyses these were combined.

Table 11 shows the prevalence rates and odds ratios (ORs) for type 2 diabetes and impaired glucose tolerance (IGT) according to weekly exercise frequency and intensity, as well as yearly energy expenditure on exercise in relation to birth size. Frequent and moderately intense exercise were both associated with lower rates of glucose intolerance. This effect was strongest in subjects whose birth weight was <3000g. There was a significant interaction between exercise frequency and birth weight ($p=0.003$). The birth weight-related positive effects of exercise did not differ within different adult BMI groups or between the sexes. Adjustment for age, parental history of type 2 diabetes or concomitant diseases did not change the findings. Strenuous exercise did not give more protection against glucose intolerance compared to moderate exercise.

Thinness at birth, assessed using ponderal index at birth, showed a similar statistically significant relationship between small birth size and all three measurements of exercise (Table 11). Yearly energy expenditure on exercise interacted significantly with ponderal index.

In males, exercise frequency correlated inversely with birth weight ($p=0.009$, adjusted for age and BMI) and ponderal index ($p=0.033$). The latter correlated inversely also with exercise intensity ($p=0.030$) and yearly energy expenditure on physical activity ($p=0.005$). Among women these associations were not significant.

Table 11. Prevalence (%) and odds ratio (95% CI) of type 2 diabetes and impaired glucose tolerance by birth size and frequency of weekly exercise, its intensity and yearly energy expenditure on exercise (geometric median 94 477 kcal/year). Total number of subjects in parentheses.

	Frequency of exercise		**Intensity of exercise**		**Yearly energy expenditure on exercise**	
	< 3 times/week	≥ 3 times/week	Light	Moderate or strenuous	Below median	Above median
Birth weight (g)						
≤3000	60% (53)	23% (44)	58% (50)	28% (46)	50% (40)	38% (53)
	5.2 (2.1-13)	**1.0**	3.5 (1.5-8.2)	**1.0**	1.6 (0.7-3.8)	**1.0**
>3000	52% (215)	47% (173)	55% (212)	43% (187)	52% (199)	47% (187)
	3.6 (1.7-7.7)	3.1 (1.4-6.6)	3.1 (1.6-6.3)	1.9 (0.9-3.8)	1.8 (1.0-3.3)	1.5 (0.8-2.7)
p-value for interaction	0.003		0.12		0.51	
Ponderal index (kg/m^3)						
≤26	55% (85)	33% (84)	57% (85)	35% (88)	56% (80)	35% (87)
	2.5 (1.3-4.6)	**1.0**	2.4 (1.3-4.4)	**1.0**	2.4 (1.3-4.6)	**1.0**
>26	52% (182)	48% (133)	55% (176)	43% (145)	49% (158)	51% (153)
	2.2 (1.3-3.7)	1.9 (1.1-3.3)	2.3 (1.3-3.8)	1.4 (0.8-2.4)	1.8 (1.1-3.1)	2.0 (1.1-3.4)
p-value for interaction	0.058		0.33		0.012	

5.4 Birth size, change in BMI in childhood and adult body composition

Table 4 shows the characteristics of the study subjects in childhood and adulthood. Correlations between key anthropometric variables at birth and in adulthood are presented in Table 12.

Childhood BMI in relation to current growth charts

According to current World Health Organization (WHO) growth charts (223), the mean BMI at birth corresponded to the 52nd and 50th percentile in boys and in girls, respectively. 2.7% and 3.7% of newborn boys and girls, respectively, were at or above the 95th percentile. At the age 2 of years, 8.7% or 7.9% of boys and 12.3% or 11.3% of girls were at or above the 95th percentile according to WHO or at or above the BMI cutoff point corresponding to a BMI of 25 at age 18 according to the International Obesity Task Force (IOTF) (224), respectively. Only the latter growth charts include the age of 11 years. At this age no one was above the BMI corresponding BMI of 30, the limit for obesity, and 0.9% of boys and 3.8% of girls were overweight (at or above the BMI corresponding to a BMI of 25 at the age of 18 years by the IOTF).

During the first two years after birth 43% of boys and 45% girls followed the same BMI percentile (gain or loss in BMI z-score <=0.67 SD), whereas 27% and 28% of boys and girls, respectively, crossed upward. Between ages 2 and 11 years 49% of boys and 46% of girls remained at the same BMI percentile, whereas 24% of them had crossed upward.

Size at birth and in adult life

Birth weight was positively related to adult BMI, but in women this relationship was dependent on adult height (Tables 12 and 13). High birth weight predicted a larger hip circumference. The positive association of birth weight with waist circumference in men disappeared after adjustment for BMI.

Weight at birth and adult body composition

Birth weight correlated strongly with adult lean mass in the unadjusted model and in the models adjusted either for age and adult height or age and adult BMI (Table 13). This association was not attenuated by additional adjustments for maternal size and

Table 12a. Pearson's correlations between birth size, adult body size and adult body composition variable in 56 to 70 year old men.

	Measures at birth		**Adult measurements**							
Men (*n*=928)	Birth weight	Length at birth	Height	Weight	BMI	Waist circumference	Hip circumference	Lean mass	Fat mass	Fat percent
Measures at birth										
Birth weight	1.00	0.82***	0.22***	0.21***	0.13***	0.11**	0.16***	0.26***	0.12***	0.02
Length at birth		1.00	0.28***	0.22***	0.11**	0.11***	0.17***	0.29***	0.10*	0.003
Adult measurements										
Height			1.00	0.40***	-0.03	0.13***	0.30***	0.68***	0.02	-0.22***
Weight				1.00	0.90***	0.90***	0.93***	0.85***	0.86***	0.65***
BMI					1.00	0.92***	0.88***	0.61***	0.93***	0.81***
Waist circumference						1.00	0.86***	0.62***	0.92***	0.81***
Hip circumference							1.00	0.75***	0.85***	0.67***
Lean mass								1.00	0.48***	0.17***
Fat mass									1.00	0.93***
Fat percent										1.00

Abbreviation: BMI, body mass index.
* $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Table 12b. Pearson's correlations between birth size, adult body size and adult body composition variable in 56 to 70 year old women.

	Measures at birth		**Adult measurements**							
Women (n=1075)	Birth weight	Length at birth	Height	Weight	BMI	Waist circumference	Hip circumference	Lean mass	Fat mass	Fat percent
Measures at birth										
Birth weight	1.00	0.80***	0.26***	0.14***	0.05	0.06	0.10***	0.23***	0.05	-0.03
Length at birth		1.00	0.32***	0.09*	-0.03	0.02	0.04	0.21***	-0.01	-0.08**
Adult measurements										
Height			1.00	0.27***	-0.11***	0.06*	0.13***	0.61***	0.03	-0.20***
Weight				1.00	0.93***	0.90***	0.90***	0.82***	0.94***	0.77***
BMI					1.00	0.91***	0.88***	0.61***	0.96***	0.88***
Waist circumference						1.00	0.79***	0.65***	0.90***	0.81***
Hip circumference							1.00	0.66***	0.90***	0.78***
Lean mass								1.00	0.59***	0.30***
Fat mass									1.00	0.93***
Fat percent										1.00

Abbreviation: BMI, body mass index.
* P<0.05; ** P<0.01; *** P<0.001.

Table 13a. Adult body size, body composition and muscle strength according to birth weight in 927 men aged 56 to 70 years. Models adjusted for age and, alternatively, height or body mass index, are also presented.

Men	Means of the adult measurement according to the birth weight group			Regression coefficients (β; with 95% confidence intervals) expressing changes in adult measurements associated with a 1 kg increase in birth weight					
				Model 1[a]		Model 2[b]		Model 3[c]	
	≤3000 g	3000-3500 g	>3500 g	β	95% CI	β	95% CI	β	95% CI
	n = 148	n = 363	n = 416						
Adult body size									
Height, cm	174.7	176.3	178.1	2.64	1.88, 3.39***	-		2.62	1.86, 3.38***
Body mass index, kg/m^2	27.0	27.3	27.9	1.00	0.49, 1.51***	1.10	0.57, 1.63***	-	
Waist circumference, cm[d]	99.2	99.4	101.1	2.2%	0.8, 3.8%**	1.7%	0.3, 3.3% *	-0.2%	-0.9, 0.4%
Hip circumference, cm[d]	100.0	100.8	102.1	2.1%	1.3, 3.0%***	1.3%	0.5, 2.2% *	0.7%	0.3, 1.1%**
Adult body composition									
Lean body mass, kg	62.0	64.4	66.6	4.07	3.07, 5.06***	1.74	0.98, 2.51 ***	2.68	1.89, 3.48***
Fat mass, kg[d]	19.1	19.1	20.1	7.1%	2.0, 12.5%**	7.4%	2.1, 13.0% **	-1.8%	-3.8, 0.2%
Percentage of fat	24.0	23.5	23.8	0.28	-0.50, 1.06	0.94	0.17, 1.72 *	-0.94	-1.38, -0.49**
Adult muscle strength									
Grip strength, kg	38.2	40.4	40.8	1.84	0.62, 3.06 **	0.47	-0.71, 1.65	1.30	0.10, 2.50*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] Unadjusted.

[b] Adjusted for age and adult height.

[c] Adjusted for age and adult body mass index.

[d] Geometric means.

Table 13b. Adult body size, body composition and muscle strength according to birth weight in 1075 women aged 56 to 70 years. Models adjusted for age and, alternatively, height or body mass index, are also presented.

Women	Means of the adult measurement according to the birth weight group			Regression coefficients (β; with 95% confidence intervals) expressing changes in adult measurements associated with a 1 kg increase in birth weight					
				Model 1[a]		Model 2[b]		Model 3[c]	
	≤3000 g	3000-3500 g	>3500 g	β	95% CI	β	95% CI	β	95% CI
	n = 248	n = 429	n = 398						
Adult body size									
Height, cm	161.5	162.5	165.0	3.16	2.45, 3.87***	-		3.17	2.47, 3.87***
Body mass index, kg/m^2	27.5	27.7	27.7	0.50	-0.15, 1.15	0.87	0.20, 1.54*	-	
Waist circumference, cm[d]	89.4	90.2	90.6	1.8%	0.0, 3.6%	0.9%	-0.5, 3.3%	-0.5%	-0.3, 1.3%
Hip circumference, cm[d]	103.0	103.6	104.6	1.9%	0.8, 3.1%***	1.4%	0.2, 2.6% *	1.2%	0.7, 1.8%***
Adult body composition									
Lean body mass, kg	46.2	47.4	49.2	2.87	2.14, 3.59***	1.02	0.41, 1.63 ***	2.54	1.97,3.11***
Fat mass, kg[d]	23.7	23.9	24.1	3.9%	-1.1, 9.1%	3.7%	-1.4, 9.1%	1.1%	-0.7, 3.0%
Percentage of fat	34.5	34.0	33.4	-0.48	-1.39, 0.43	0.32	-0.60, 1.24	-0.93	-1.36, -0.50***
Adult muscle strength									
Grip strength, kg	21.4	23.1	23.6	1.79	0.94, 2.64 ***	0.74	-0.11, 1.60	1.54	0.68, 2.39***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] Unadjusted.

[b] Adjusted for age and adult height.

[c] Adjusted for age and adult body mass index.

[d] Geometric means.

age, gestational age, smoking status, physical activity, and social class in childhood and adulthood.

Fat mass and distribution were not consistently related to birth weight. In men high birth weight was related to greater fat mass in unadjusted and height-adjusted models but unrelated in a BMI-adjusted model; in women there was no significant association between birth weight and fat mass. On the other hand, higher fat percentage was predicted in the BMI-adjusted model by lower birth weight.

The association of birth weight with adult body fat percentage in men depended on the level of adult BMI (p for interaction birth weight*adult BMI = 0.002) as shown in Table 14. Low birth weight was associated with higher body fat percentage only in those with a BMI below 30 kg/m^2. In men with a BMI over 30 kg/m^2 this trend seemed to reverse although this did not reach statistical significance. In women the interaction between the effects of birth weight and adult BMI on fat percentage was not statistically significant (p = 0.56).

Table 14. Adult body fat percentage (n) according to birth weight in different categories of adult body mass index (BMI).

	Adult BMI (kg/m^2)		
	<25 kg/m^2	25-30 kg/m^2	>30 kg/m^2
Men			
Birth weight			
≤3000 g	19.4 (41)	24.5 (78)	29.5 (29)
3000-3500 g	18.1 (101)	23.6 (187)	30.5 (74)
>3500 g	18.0 (100)	23.2 (213)	30.9 (103)
Regression coefficient	-1.18	-1.11	0.89
(95% CI)	(-2.19 to -0.16)	(-1.85 to -0.36)	(-0.32 to 2.09)
p for trend	0.042	0.012	0.15
Women			
Birth weight			
≤3000 g	27.9 (88)	34.8 (98)	43.0 (62)
3000-3500 g	27.4 (135)	34.1 (173)	41.2 (121)
>3500 g	26.6 (124)	33.9 (163)	40.9 (110)
Regression coefficient	-1.25	-0.61	-0.90
(95% CI)	(-2.38 to -0.13)	(-1.33 to 0.12)	(-2.0 to 0.21)
p for trend	0.030	0.10	0.11

p = 0.002 for interaction between birth weight and categories of BMI in men; p = 0.56 in women

Change in BMI in infancy and childhood in relation to adult body composition

Figure 4 shows the relationship between childhood BMI and adult outcome variables. In both sexes, a higher adult BMI was predicted by higher BMI throughout childhood. Similarly, a higher BMI during childhood predicted a higher lean mass index (LMI) in adulthood.

Because we aimed to examine to what extent a change in BMI in different periods of growth was related to adult body components, next we used conditional measures which are mutually uncorrelated by construction. This measure tells whether change in childhood BMI between two ages is greater or less than would be expected from BMIs at earlier ages, rapid gain meaning crossing from an original growth percentile in this population to a higher one. Table 15 shows that, independently of each other, a higher BMI at birth and a higher gain in BMI during each period analyzed were associated with a higher LMI in adulthood. For example, a 1 SD increase in conditional BMI between birth and 1 year of age was related to a 0.17 kg/m^2 and 0.22 kg/m^2 increase in adult LMI in men and women, respectively.

Figure 4 shows that adult fat mass index (FMI) was predicted by a higher BMI later in childhood. Accordingly, a higher FMI was predicted by a higher gain in BMI between 2 and 7, and 7 and 11 years, but not by BMI at birth or change in BMI between birth and 2 years (Table 15). Body fat percentage and waist circumference showed similar associations.

Adult body composition in relation to age, lifestyle and maternal characteristics

In Study IV, higher age was associated with lower adult lean mass in men ($p<0.001$) but not in women. Physical activity or smoking were not associated with lean body mass. Lower age ($p=0.016$ in men and $p=0.007$ in women), frequent physical activity ($p<0.001$), higher social class in childhood ($p<0.001$ in men and $p=0.031$ in women) and in adulthood ($p<0.001$) were associated with a lower body fat percentage. We calculated maternal BMI from height and weight measured before delivery. Lower maternal height ($p<0.001$), lower maternal BMI ($p=0.008$ in men and $p=0.002$ in women) and lower maternal age at delivery ($p=0.024$ in men) were associated with a lower lean mass of the adult offspring. In women, taller maternal height ($p=0.001$) and higher maternal BMI ($p<0.001$) predicted a lower body fat percentage. Gestational age at birth and mother's parity (firstborn or other) had no effect on outcomes.

In Study V, a simultaneous regression with age, physical activity level, smoking status and social class in childhood and adulthood showed that LMI was lower by higher age in men (β = -0.06 kg/m^2 per year, 95% CI -0.11, -0.02, $p<0.006$). In

FIGURE 4 Cross-sectional Pearson's correlation coefficients of adult body mass index (BMI), lean mass index and fat mass index with BMI at each birthday between 0-2, and 6-11 years, with the points connected for ease of reading. Values are adjusted for adult age and shown for men and women separately; dashed lines connect the 95% confidence limits.

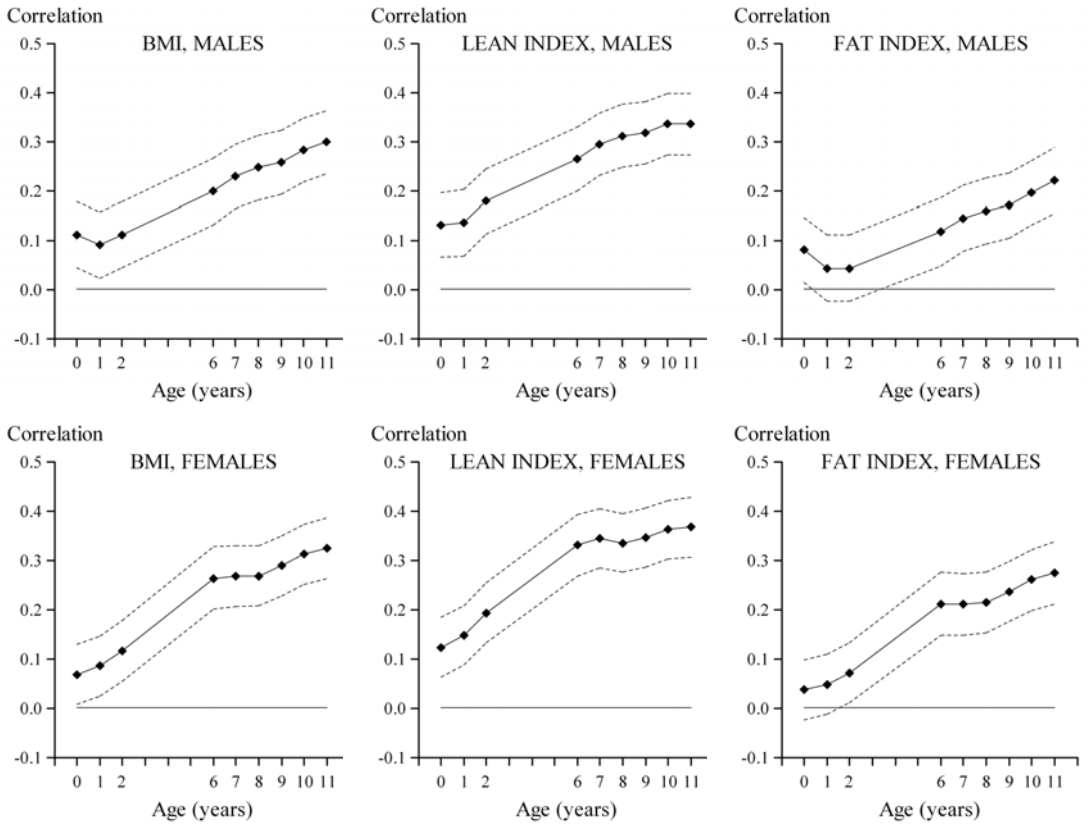

Table 15a. Body mass, lean mass and fat mass indices at the age of 56-70 years according to tertiles of body mass index (BMI) at birth and change in BMI up to the age of 11 years in men. Linear regression coefficients indicate how many units each dependent variable changes by a difference of 1 SD in BMI at birth or a 1 SD increase in conditional BMI between selected ages.

MEN	BMI (kg/m^2)	Lean mass index (kg/m^2)	Fat mass index (kg/m^2)
BMI at birth (n=875)			
1 lowest	27.2	20.5	6.6
2 middle	27.4	20.6	6.7
3 highest	27.9	21.0	6.8
Regression coefficient	0.44	0.24	0.21[2]
(95% CI)	(0.18 to 0.70)	(0.13 to 0.36)	(0.04 to 0.38[2])
p for linear trend [1]	0.001	<0.0001	0.02[2]
BMI at 1 year adjusted for BMI at birth (n=875)			
1 lowest	27.3	20.6	6.7
2 middle	27.4	20.7	6.6
3 highest	27.8	20.9	6.8
Regression coefficient	0.23	0.17	0.06
(95% CI)	(-0.03 to 0.49)	(0.06 to 0.29)	(-0.12 to 0.23)
p for linear trend [1]	0.08	0.003	0.5
BMI at 2 years adjusted for BMI at 1 year (n=875)			
1 lowest	27.1	20.4	6.6
2 middle	27.8	20.8	6.9
3 highest	27.7	20.9	6.7
Regression coefficient	0.22	0.21	0.01
(95% CI)	(-0.04 to 0.48)	(0.09 to 0.32)	(-0.16 to 0.19)
p for linear trend [1]	0.1	0.001	0.9
BMI at 7 years adjusted for BMI at 2 years (n=842)			
1 lowest	26.6	20.2	6.4
2 middle	27.3	20.7	6.6
3 highest	28.5	21.3	7.1
Regression coefficient	0.87	0.44	0.44
(95% CI)	(0.61 to 1.13)	(0.32 to 0.55)	(0.26 to 0.61)
p for linear trend [1]	<0.0001	<0.0001	<0.0001
BMI at 11 years adjusted for BMI at 7 y (n=811)			
1 lowest	26.7	20.4	6.3
2 middle	27.4	20.7	6.7
3 highest	28.3	21.1	7.2
Regression coefficient	0.73	0.32	0.41
(95% CI)	(0.47 to 1.00)	(0.20 to 0.43)	(0.24 to 0.59)
p for linear trend [1]	<0.0001	<0.0001	<0.0001

[1] Adjusted for age.

[2] When geometric means are used (skewness corrected), the regression coefficient is 1.9% (-0.6% to 4.4%, p=0.1).

Table 15b. Body mass, lean mass and fat mass indices at the age of 56-70 years according to tertiles of body mass index (BMI) at birth and change in BMI up to the age of 11 years in women. Linear regression coefficients indicate how many units each dependent variable changes by a difference of 1 SD in BMI at birth or a 1 SD increase in conditional BMI between selected ages.

WOMEN	BMI (kg/m^2)	Lean mass index (kg/m^2)	Fat mass index (kg/m^2)
BMI at birth (n=1022)			
1 lowest	27.6	17.7	9.6
2 middle	27.1	17.9	9.5
3 highest	28.4	18.2	9.9
Regression coefficient	0.31	0.20	0.11
(95% CI)	(-0.003 to 0.62)	(0.10 to 0.30)	(-0.12 to 0.34)
p for linear trend [1]	0.05	0.0001	0.4
BMI at 1 year adjusted for BMI at birth (n=1022)			
1 lowest	27.4	17.7	9.6
2 middle	27.5	17.9	9.5
3 highest	28.2	18.2	9.9
Regression coefficient	0.38	0.22	0.17
(95% CI)	(0.07 to 0.69)	(0.12 to 0.32)	(-0.06 to 0.40)
p for linear trend [1]	0.02	<0.0001	0.2
BMI at 2 years adjusted for BMI at 1 year (n=1022)			
1 lowest	27.3	17.7	9.4
2 middle	27.6	17.9	9.5
3 highest	28.3	18.2	10.0
Regression coefficient	0.38	0.20	0.19
(95% CI)	(0.08 to 0.69)	(0.10 to 0.30)	(-0.04 to 0.42)
p for linear trend [1]	0.02	0.0001	0.1
BMI at 7 years adjusted for BMI at 2 years (n=972)			
1 lowest	26.8	17.5	9.2
2 middle	27.4	17.9	9.3
3 highest	28.9	18.4	10.4
Regression coefficient	1.21	0.46	0.74
(95% CI)	(0.89 to 1.52)	(0.36 to 0.57)	(0.51 to 0.98)
p for linear trend [1]	<0.0001	<0.0001	<0.0001
BMI at 11 years adjusted for BMI at 7 y (n=936)			
1 lowest	26.5	17.6	8.9
2 middle	27.6	17.9	9.5
3 highest	28.9	18.2	10.5
Regression coefficient	0.93	0.26	0.66
(95% CI)	(0.62 to 1.24)	(0.16 to 0.36)	(0.43 to 0.89)
p for linear trend [1]	<0.0001	<0.0001	<0.0001

[1] Adjusted for age.

women LMI was lower by higher social class in adulthood (p=0.003). Higher FMI was predicted by physical inactivity (p<0.0001), by lower social class in adulthood (p=0.03 in men and 0.0005 in women), in men by non-smoking (p=0.02) and lower social class in childhood (p=0.0003), and in women by higher age (p=0.004). Neither in Study IV nor in Study V did the adjustment for these variables change the relationships between birth size or childhood growth and adult body composition.

Grip strength in relation to adult characteristics and size at birth

Among the 56 to 70 year old subjects measurements related to lean mass were positively associated with grip strength. For example, a one kilogram increase in lean mass corresponded in men to a 0.38 kg (95 % CI: 0.31, 0.46, p<0.001) and in women to a 0.29 kg (95 % CI: 0.22, 0.35, p<0.001) increase in grip strength. Fat percentage was inversely associated with grip strength in men (0.23 kg per unit, 95 % CI: 0.33, 0.12, p < 0.001). Other factors related to lower grip strength were higher age and smoking. A one year increase in age corresponded to a 0.7 kg (95 % CI: 0.5, 1.0) and a 0.5 kg (95 % CI: 0.4, 0.6) decrease in grip strength in men and women, respectively, and male and female smokers had 1.6 kg (95 % CI: 0.2, 3.1) and 1.5 kg (95 % CI: 0.4, 2.6) lower grip strength than non-smokers, respectively.

Grip strength was related to birth weight. A one kilogram increase in birth weight corresponded to a 1.8 kg increase in grip strength in both men and women (95 % CI: 0.6, 3.1 in men and 0.9, 2.6 in women, Table 13). This association disappeared after adjustment for height (Table 11) and in men also after adjustment for the amount of lean mass (0.03 kg, 95% CI: 1.2, 1.2). In women this association diminished after adjustment for lean mass (0.9 kg, 95% CI: 0.03, 1.8, p=0.042).

6 DISCUSSION

6.1 Birth size and adult health

6.1.1 Birth size and adult blood pressure level

Small body size at birth was associated with higher systolic BP in men and women aged 65-75 years. In the total sample, the increase in systolic BP associated with a 1 kg decrease in birth weight was small, 3.5 mmHg, which is similar to what has been shown previously (50; 146).

A novel finding, however, was that in these elderly people this association was only present among those who had hypertension. Among them the inverse association between birth weight and systolic BP was more remarkable: a 1 kg increase in birth weight was associated with a 6.4 mmHg decrease in systolic BP recorded at the clinic. Consistent with this finding, two other studies have reported missing or weaker inverse association between birth weight and systolic BP among people without antihypertensive treatment compared to people on treatment or the combined group of those who had never taken antihypertensive drugs and those who had (155; 156).

The evidence on the inverse association between size at birth and BP in adulthood is based on office BPs. While traditionally interpreted as supporting the hypothesis of permanently raised resting BP levels originated *in utero*, differences in office BP levels might as well reflect reactivity to a stressful situation, so-called "white-coat hypertension". This type of mechanism, which is, however, not exclusive of other hypertensive disease pathways, has been presented in subjects exposed to famine *in utero* in whom BP response to stress was increased (96). Instead, ambulatory measurements give a picture of BP over a 24-hour period. In our study the findings from BPs measured at the clinic were confirmed with ambulatory measurements made on a subsample. Reassuringly, the clinic and averaged ambulatory measurements were highly correlated. Furthermore, comparably to our findings on birth size and office BP, among all study subjects a 1 kg increase in birth weight was associated with a 3.9 mmHg decrease in mean systolic ambulatory BP and, again, this association with a 9.4 mmHg decrease was confined to people with hypertension. This large difference occurred despite the subjects being on treatment for hypertension. These findings were not repeated in a study on quartiles of birth weight in relation to ambulatory measurements in 70-year-old men, of whom 24% were treated for hypertension (156).

There were no similar trends with diastolic pressure. With increasing age, pulse pressure widens through rising systolic pressure. Diastolic pressure does not tend to rise, and one would not therefore expect it to be linked to self-perpetuating processes that act on blood pressure and are associated with aging. In accordance with our results, previous studies have reported weak or lacking associations of birth weight with diastolic BP (153). Furthermore, presumably many studies have not presented data on diastolic BP because of lack of a significant association.

Another novel finding was that the inverse association between birth weight and systolic BP level among hypertensive people was confined to people with the Pro12Pro polymorphism of the PPAR-γ2 gene (9.3 mmHg/1 kg,). This finding underscores the importance of genetic background and gene-environment interactions on the association of early growth and adult health, and guides further research on the mechanisms behind these associations, given the important role of this gene in the control of energy, glucose and lipid homeostasis. Because of the high prevalence of the Pro12Pro polymorphism (68% of all and a similar percentage of hypertensive subjects in our study sample) (164), even a small effect interacting with birth weight on BP translates into a large risk at the population level.

6.1.2 Programming of hypertension; suggested background mechanisms

Self-perpetuating cycle initiated in utero and amplified by age-related damage

In addition to systolic BP level, birth size has been associated with established hypertension (126). In that study in the Helsinki Birth Cohort, people were defined hypertensive if they were receiving reimbursement for antihypertensive medication, which in Finland is reserved for those with more severe or complicated hypertension. They were shown to have lower birth weight and shorter body length at birth than did other people (126). The present results were consistent with this association with established hypertension, and the hypothesis that slow growth *in utero* initiates a self-perpetuating mechanism that leads to hypertension.

The results suggest that during early adult life the various regulatory mechanisms controlling BP ensure that the pathological processes associated with poor fetal growth lead only to a small increase in BP. In older people, however, damages related to age begin a vicious cycle of rising BP, further damages, and eventually the development of hypertension, amplified by the self-perpetuating cycle. People with lesions acquired *in utero* are more vulnerable to this process, and the inverse association between birth weight and BP becomes focused on this group. This framework of ideas may illuminate the paradox that low birth weight has only small effects on BP levels in the general population (50), but has large effects on age-

related risk of hypertension and morbidity and mortality from cardiovascular disease (12; 13). However, according to the Uppsala studies, mortality from cardiovascular disease is not mediated directly through an increased blood pressure in men with low birth weight (225).

Two possible self-perpetuating mechanisms involve nephron numbers and arterial elastin. The number of nephrons each person has at birth varies widely, from 300 000 to 1 100 000 (226). Small babies have fewer nephrons, which, combined with age-related nephron loss, could lead to a self-perpetuating cycle of rising BP and nephron loss (97; 99). Alternatively, people who were small at birth have been shown to have less elastic arteries (103). The elasticity of larger arteries depends on the scleroprotein elastin, which is laid down *in utero* and during infancy and thereafter turns over slowly. Its half-life in humans is approximately 40 years. Reduced elastin deposition in small babies leads to stiffness in the major arteries, which leads to raised pulse pressure. The loss of elastin with aging will amplify this increase in pulse pressure. It can readily be shown that stiffer, less compliant arteries alter the pressure wave generated by the contraction of the heart in such a way that systolic BP increases while diastolic BP tends to fall (227).

Since the ambulatory BP recording was performed during ongoing treatment, higher systolic BP in hypertensive subjects with low birth weight compared with those with high birth weight may be interpreted as a weaker response to antihypertensive medication. Among these hypertensive people on medication, a majority received beta-adrenergic receptor blockers and 44% diuretics while approximately one third received either calcium channel antagonists or ACEI/ARBs, 49% being on combination therapy. The degree of response to different antihypertensive medications may guide the search for possible pathophysiologic mechanisms behind the association of low birth weight and high BP in later life. Unfortunately, in our study the numbers of people on different medications with available ambulatory recordings were too small to assess the BP responses according to birth size. This kind of study would also require a prospective setting with a recent onset of hypertension and preferably only one class of medication in use at a time.

Gene-environment interactions

The self-perpetuating cycle may be further modified by interactions between gene polymorphisms and early environment. Low birth weight has been shown to have a large effect on insulin resistance among people with the common Pro12Pro polymorphism of the PPARγ2-gene (164). We showed that low birth weight also had a strong effect on systolic BP levels in hypertensive Pro12Pro carriers but not in hypertensive carriers of the Ala-allele. A synthesis of these two observations might be that insulin resistance influences the renin-angiotensin-aldosterone system, which

has been perturbed by the reduced nephron numbers that accompany small body size at birth (97; 99; 100). Insulin up-regulates angiotensin II type 1 receptor gene expression, leading to enhanced signalling by angiotensin II, which is a potent vasoconstrictor (228). Angiotensin II inhibits insulin signalling (229; 230), which may further increase insulin resistance, leading to a vicious cycle of rising blood pressure and increasing insulin concentrations.

The importance of renin-angiotensin-aldosterone system in the development of hypertension linked to early growth is further highlighted by our finding that among people on antihypertensive medication people with low birth weight were more likely to be receiving ACEI/ARB. This is consistent with previous findings on Caucasian men (157). This association, and a similar one with birth length, was, again, confined to people with the Pro12Pro polymorphism. If blood pressure levels in these people are elevated by an interaction between insulin resistance and the renin-angiotensin-aldosterone system, ACEI/ARB might be an appropriate therapy. This could not be tested in our cross-sectional setting. Another possible explanation for the use of ACEI/ARB in people who had low birth weight is that low birth weight is linked to co-morbid conditions such as myocardial infarction, congestive heart failure and type 2 diabetes that indicate the use of these medications. However, also animal experiments suggest a role of the renin-angiotensin system in the pathogenesis of hypertension that is attributable to experiences *in utero* (45; 231).

The hypothesis of fetal programming has been challenged by an alternative explanation, the fetal insulin hypothesis. This hypothesis suggests that genetically determined insulin resistance may lead to both low birth weight and increased risk of hypertension, atherosclerosis and type 2 diabetes in adult life (232). The common genetic background would therefore explain the association between low birth weight and insulin resistance. As the insulin-sensitizing Ala-allele of the PPARγ2 gene has been associated with higher birth weight and ponderal index (233), this gene is a potential candidate gene to test this hypothesis. In our study and in a German study (234) the Pro12Ala polymorphism was not related to higher birth weight. However, only among those with small body size at birth, the carriers of the Ala-allele were protected against insulin resistance (235), indicating gene-environment interaction since fetal life, rather than common genetic background for low birth weight and insulin resistance. As the hypotheses are not mutually exclusive, the role of genes and gene polymorphisms in programming deserves more attention.

Adult body size and blood pressure; role of birth size

The strong association between high current BMI and elevated BP has been described repeatedly. In our study this association was confined to people who were not hypertensive. Similarly, the strong associations between elevated BP and large

waist circumference and high percentage body fat were confined to normotensive people. The absence of an association between indicators of obesity and BP in hypertensive patients suggests that a reduction in body fat might be of less importance in relation to BP control in aged hypertensive patients than it is in the general population. However, it is well established that weight control and reduction in cardiometabolic risk improvement is essential. Plausibly the effects of high fat mass on raised BP are masked in these 65-75 year old hypertensive subjects by the effects of the self-perpetuating processes linked to poor growth *in utero*.

6.1.3 Birth size and glucose tolerance; role of regular physical activity

Regular and moderate habitual exercise protected against glucose intolerance in elderly people who were at increased risk of developing type 2 diabetes because they were born thin or small. The sufficient intensity of exercise was comparable to brisk walking.

Despite the different dichotomization of leisure-time physical activity, these results are in line with another study on middle-aged Finnish men in whom the associations of thinness at birth with fasting insulin and glucose levels, the insulin sensitivity index and the metabolic syndrome, detected in the whole study group, were absent in men engaging in at least 25 min/week of strenuous leisure-time physical activity (130). In more sedentary men the association of thinness at birth with hyperinsulinemia was enhanced making the interaction of physical activity and the ponderal index significant. In that study objectively measured cardiovascular fitness also modified these associations comparably. In another study physical activity in low birth weight subjects did not reduce the risk of having at least two components of the metabolic syndrome (133). Because that definition did not necessarily include glucose intolerance, which was defined as HbA1c $\geq$ 6.2%, the results are not fully comparable. In addition, younger age (mean of 36 years), inclusion of other than leisure-time activity such as work-related activities, and use of self-reported birth weights may explain why there was no reduction in the risk.

Insulin resistance is an important and rapidly increasing condition worldwide and is potentially the underlying pathophysiological factor for a large number of chronic diseases, like the metabolic syndrome, type 2 diabetes and cardiovascular disease. Although genetic and early environmental factors are of importance in the development of insulin resistance, the main determinants are modifiable lifestyle factors. Treatment and prevention of insulin resistance and glucose intolerance in high risk groups for type 2 diabetes is possible by regular and adequate exercise (185). Physical activity recommendations should be targeted specifically towards people who are likely to benefit particularly from exercise but first they need to be

identified. In this study people who were small at birth, and thus at high risk for glucose intolerance, gained a special benefit from exercise and should therefore be encouraged to maintain an active lifestyle. The exercise intensity that was needed is reasonable for most people.

In addition to general insulin resistance and type 2 diabetes, a small body size at birth is associated with muscular insulin resistance (1; 107; 109; 236). Improved insulin sensitivity, in turn, is central to the protective effect of exercise against type 2 diabetes (185; 237-239) and might explain our findings. This is supported by the aforementioned study by Laaksonen et a. 2003 (130): the adverse effect of thinness at birth on a proxy for insulin resistance, the level of fasting insulin, was no longer evident in physically active men. Physical activity, by improving muscular insulin sensitivity through a variety of mechanisms, may be particularly beneficial for individuals born small and thus at risk for insulin resistance.

The state of insulin resistance because of altered muscle metabolism in people born small may be further enhanced because of their lower lean mass which consists mainly of muscle mass. This is discussed in Chapter 6.1.4. At any level of adult BMI, people who were small at birth had a higher ratio of fat to lean body mass (114). Since muscle tissue is the most important tissue for the storage and oxidation of glucose, individuals with a higher fat to muscle ratio are at increased risk of the metabolic consequences of insulin resistance.

Small body size at birth has been associated with not only changes in muscle mass and function but also with a reduced cardiopulmonary capacity (1), which theoretically could influence willingness to exercise. Indeed, in 12 year old subjects birth weight and aerobic fitness were positively related (186), but, however, in middle-aged Finnish men thinness at birth was not associated with physical activity or cardiorespiratory fitness (130). We did not measure fitness, but, interestingly, in our study elderly men with a small body size at birth exercised more frequently and with higher intensity than the men with a larger body size at birth. In our elderly high-risk subjects, this might represent the survival of the fittest.

6.1.4 Birth size, change in childhood BMI and adult body composition

Adult body composition was assessed by a bioelectrical impedance analysis (BIA). In men and women aged 56 to 70 years birth weight was positively related to adult lean body mass. The finding remained consistent after adjustment for body size, which is known to be associated with birth size, or confounding factors affecting the amount of lean mass such as physical activity, smoking and maternal height or BMI. During childhood the timing and magnitude of gain in standard deviations for BMI

had a significant impact on the adult body fat and lean compartments. High BMI at birth, rapid gain in conditional z-scores for BMI in infancy, and in early and late childhood up to the age 11 years, were independently related to higher adult height-normalized lean mass index, LMI. Higher adult fat mass index (FMI) was predicted only by rapid increase in BMI beginning after 2 years of age. These findings provide further insight into the mechanisms that underlie the link between low birth weight or thinness at birth, childhood growth patterns and adult health outcomes.(143; 188-190; 192)

Lean mass

The results of Studies IV and V are consistent with previous studies linking low birth weight with reduced lean body mass (111-117). Correspondingly, as in Study V, rapid childhood growth throughout childhood has been related with higher lean mass in later life (211-213).

Fat mass

High birth weight has been linked in a number of previous studies to high adult BMI which is a commonly used and reasonably valid index of fatness in population studies (143; 188-192). This has been counterintuitive, since whereas obesity has long been known to predispose to several diseases, including type 2 diabetes and cardiovascular disease, accumulating evidence has linked higher birth weight with a lower risk of these diseases (16; 126; 127). However, because BMI represents both lean and fat mass, a high BMI at an individual level does not necessarily indicate increased adiposity. The limitations of BMI and the need for more specific measures of adiposity are increasingly recognized as illustrated by our study which used BIA to estimate total fat mass and body fat percentage.

In Study IV birth weight was positively related to adult fat mass in men, but this association disappeared after adjustment for adult BMI. On the other hand, when current BMI was taken into account, it was low birth weight, not high, that predicted in both sexes higher adult body fat percentage. In comparison, a study on elderly men at both ends of the birth weight distribution showed that men in the low-birth-weight group had higher body fat percentage than men in the high-birth-weight group both before and after control for BMI (117). While our result suggests that the positive relationship of birth weight with adult BMI may not adequately predict the level of fatness, the impact of birth weight on fat percentage was relatively small and confined to men with a BMI below 30 kg/m2 and women with a BMI below 25 kg/m^2. This might be partly explained by non-optimal adult lifestyle, including unhealthy dietary and exercise habits, leading to excess fat mass which overrides the effects of birth weight on fat percentage in obese individuals.

We found no relationship between infant or childhood growth rate before the age of 2 years and adult fat mass, which is in contrast with three other studies (211-213). However, supporting the relative importance of rapid growth during later childhood in the development of adult fat mass, one of these studies reported that rapid gain in BMI early in childhood was more strongly related to lean mass than to adiposity in later life whereas another showed that rapid weight gain during later childhood, from 4 years onwards, was associated with the ratio of fat to lean. The dissimilarities in these studies might be explained to some extent by younger age, slenderness, different methodology, nutritional status of the population, and ethnic background of the subjects in these studies. We emphasize that in our study the adult adiposity-related increase in expected growth rate between the ages 2 and 7 may have happened at any age during this period. This period was not split up into shorter ones because the limited number of measurements between 2 and 7 years might have introduced error. The age of increase in growth rate may differ between sexes: in the Fels Longitudinal Study the BMI values diverged at age 3 years in boys and 9 years in girls between adults (mean age 51 years) who became or did not become obese (BMI $\geq$ 30) (240). We also stress that, despite the adult adiposity-related rapid gain in BMI between 2 and 11 years of age, only a small minority of our subjects were overweight and none were obese as children according to the contemporary BMI references (224).

Waist circumference

Waist circumference has been suggested as a reasonable indicator of visceral fat in studies validating anthropometric measures against abdominal computerized tomography (241). Two other studies have assessed, in European subjects, the relationship between birth weight and waist circumference unadjusted and adjusted for BMI (202; 204). Consistent with these studies, we found a positive association between birth weight and waist circumference in men (202; 204) but not in women (204). This association remained significant after adjustment for BMI in one study (204).

Grip strength

We extended the assessment of early life origins of adult body composition to that of muscle strength. As could be expected from the strong relationship between birth weight and lean mass - which consists mainly of muscle mass - grip strength was stronger by higher birth weight. The results on grip strength in itself were comparable with a previous study on Californian population (242) but lower than in a British cohort (243), the members of which were 3-17 years younger than our subjects. The association between birth weight and grip strength has been observed previously (116; 243; 244). Two of these studies reported adjustments for adult height and weight which did not explain the birth weight association (243; 244). We

found that this relationship disappeared after adjustment for lean mass, suggesting that the effects of prenatal conditions, indicated by birth weight, on muscle strength are mediated through effects on gross muscle mass.

Public health implications

Low birth weight is an established risk factor for type 2 diabetes and cardiovascular disease (16; 64; 127) which are leading causes of morbidity and mortality in western countries. Developmental alterations in body composition have been suggested as one of the mechanisms behind this increased risk. In these 56-70 year old men and women, high birth weight or BMI, and rapid gain in BMI before the age of 2 years, predicted higher lean mass but not fat mass, whereas rapid growth thereafter was related to relatively larger increase in fat mass; fetal or infancy poor gain in weight or BMI might predispose to disproportionately low adult lean mass. Since lean mass consists primarily of muscle tissue, which is a major site for insulin-mediated glucose metabolism, low lean mass may further predispose to an early and central feature of the cardiometabolic disorders, reduced insulin sensitivity.

A growth pattern with poor fetal or infant growth followed by later catch-up in weight or BMI seems to aggravate the risk of insulin resistance (19; 70; 171; 197; 199-201; 245) and adverse adult health outcomes including glucose intolerance and coronary heart disease (13; 64; 65; 71; 74; 246). Consistently, studies from countries undergoing the nutritional transition have shown that growth failure in early childhood together with development of overweight in later childhood is associated with several cardiometabolic risk factors in early adulthood (247). There may be critical windows for consequences of changes in growth rate: a recent study in obese 10-year old children showed that high weight gain between birth and 2 years of age, independent of birth weight, increased insulin sensitivity whereas high weight gain after 4 years of age favored insulin resistance (144). According to Study V, after the age of 2 years a rapid gain in BMI favors accumulation of fat mass. Since adipose tissue has been acknowledged as a metabolically active tissue secreting several agents that regulate processes involved in carbohydrate and fat metabolism (248), dysfunction of increased fat mass, particularly in subjects with low compensatory lean mass due to slow fetal and infancy growth, may thus induce insulin resistance promoting the development of type 2 diabetes and cardiovascular disease.

These studies illuminate the limitations of BMI as an indicator of fatness in life course studies assessing the relationship between early growth and obesity. Higher risk of obesity in later life, as assessed mainly by BMI, has been associated with rapid weight gain in infancy (60; 142; 249-251). In the Helsinki Birth Cohort Study the growth pattern leading to obesity was different from that related to cardiometabolic diseases: children who later gained weight to exceed a BMI 30 in

adult life had above-average and increasing z-scores for BMI at all ages from birth to 12 years of age (143). However, since BMI does not distinguish between lean and fat mass, studies assessing obesity by BMI should be interpreted with caution. Studies IV and V showed that high birth weight, and rapid weight or BMI gain throughout infancy and childhood, predicted higher adult lean mass and thus increased the likelihood of exceeding the obesity cut-off of BMI. The limitations of BMI as an outcome measure in studies assessing obesity has also been illustrated in children and adolescents aged 8 to 18 years, in whom increases in BMI percentile across the whole range reflected uniform increases in fat free mass, whereas percent body fat tended to increase dramatically only at higher BMI percentiles (252). That study also suggested that, even in the overweight range, BMI may reflect different degrees of fatness in boys versus girls and in younger versus older children.

A key difference between obese subjects who are metabolically healthy and those who have diabetogenic and atherogenic metabolic abnormalities might be abdominal obesity (253), specifically accumulation of visceral fat, which is closely related to insulin resistance (254; 255). A period of pre- or postnatal poor growth has been shown to alter metabolism to favor abdominal fat deposition (208) and fat gain instead of gain in lean mass during later growth (120; 208), thus possibly promoting the development of insulin resistance. Consistent with this hypothesis, the association between insulin resistance and low birth weight or thinness at birth has been shown to be amplified in subjects whose small size or thinness at birth was followed by later catch-up growth in BMI, independently of the development of actual obesity (19; 70; 171; 197; 199-201). In Study V, independent of earlier growth, a period of more rapid gain in BMI after, but not before the age of 2 years, predicted higher adult waist circumference which is a widely used proxy for abdominal obesity. However, the positive association between birth weight and waist circumference in men might seem to contradict with the hypothesis of low birth weight as a predictor of abdominal obesity. We believe that this discrepancy illustrates the importance of the use of specific indicators of body composition and fat distribution in life course studies; waist circumference cannot distinguish metabolically benign subcutaneous fat from metabolically dangerous visceral adipose tissue. Therefore we propose caution before drawing any conclusions on a question which would require more accurate methods such as computer tomography or magnetic resonance imaging to assess visceral fat.

Grip strength in elderly people is an important indicator and predictor of frailty (256). The positive association between birth weight and grip strength suggests that early life programming may have an important role, not only in the development of cardiovascular disease and type 2 diabetes, but also in determining the frames of functional capacity in ageing individuals. The importance of this is growing due to the

continuous rise in life expectancy during the last decades (257). In addition to grip strength, the balance of fat and lean mass is important for functional ability at an older age (242; 258), and according to a prospective study in 60-year old men, mortality increases as a function of percentage of fat and decreases as a function of fat-free mass (259). However, the most important factor for physical performance and functional independence at an old age is the maintenance of physical activity (260).

6.2 Limitations of the study

6.2.1 Study design

The developmental model of the origin of adult health and disease has prompted the kind of studies that explore the data on early growth in relation to adult outcomes. The observations in these clinic epidemiological studies are cross-sectional, and the detected associations do not indicate causality. Studies analyzing data on the two distant parts of the life span serve as surrogate for follow-up studies, which in this framework, considering the decades in between, are impractical. The suggested mechanisms can be tested by e.g. animal models. By combining data from different approaches we can advance the knowledge on the life course concept.

6.2.2 Study population

Subjects in these studies may not be representative of the general population born in Helsinki. The data is restricted to men and women who were born as singletons in the University Hospital, went to school in Helsinki, did not emigrate and were still alive in 1998-2003 (Studies I-III) or in 2001-4 (Studies IV-V) and willing to participate. In addition, members of the younger cohort belong to the approximately 60% of children who had attended the voluntary child welfare clinics. Regarding blood pressure and glucose tolerance status, we found it appropriate to study 65-75 year old subjects since those predisposed to have hypertension or glucose intolerance are likely to have manifested these disorders by that age. On the other hand, by that age those people who were most susceptible to cardiovascular disease may already have died, creating a survivor's bias. Similarly, our results could further be influenced by preferential survival of subjects with particular profiles of birth weight, growth profile, body composition, glucose and insulin metabolism, and blood pressure. However, our findings are based upon internal comparisons within the sample and are unlikely to be attributed to selection bias.

In Studies I and II the subsample on which the ambulatory blood pressure recording was performed was selected through the availability of monitoring equipment on the day of clinic attendance. The subsample may not have been representative of the study sample but their birth measurements, adult BMI and the proportion of hypertensive people were similar.

Since the raise in BP level with early origin seems to be amplified by age (50), our findings on blood pressure and hypertension may be limited to elderly populations. Another concern is that these studies may have limited applicability to contemporary cohorts. Intergenerational effects may have modified the results; factors causing low birth weight may differ from those operating in contemporary cohorts, e.g. maternal smoking was rare. Men and women from the younger cohort were children around the Second World War and some of them may have suffered from food shortages. In addition, concerning Studies IV-V, children from historical cohorts may have different fatness for a given BMI compared with contemporary children (261).

In Study I, classification as hypertensive was based on a self-reported diagnosis of hypertension by a physician; 18% were not currently on antihypertensive medication. Self-reported diagnosis may not be considered as reliable. However, when we classified subjects according to the use of antihypertensive medication or by clinic systolic BP ≥160 mmHg, the findings remained similar. Lower levels of clinic systolic BP categorized the majority of the people as hypertensive but the interaction between birth weight and hypertension on BP remained.

In Study II, all the subjects who reported the use of antihypertensive medication, irrespective of diagnosis, were included in the analyses. As an example, some of them may have used beta-adrenergic receptor blockers for coronary heart disease and not for hypertension. Also in this case the definition of hypertension was unlikely to cause bias since the findings remained stable when we excluded people without a diagnosis of hypertension.

82 of the 208 hypertensive subjects were receiving 2 or more antihypertensive agents, which may have affected our results on the relationship between birth size and the use of antihypertensive medication. However, in those on monotherapy, both in the whole study sample and in the Pro12Pro carriers, the relationship between birth size and the use of ACEI/ARB could be detected despite the small number (16 and 15, respectively) of these subjects.

6.2.3 Measurements

The estimate of blood pressure level was based on a mean of two consecutive measurements in the same morning, with medication taken during the previous day.

An optimal estimate would require measurements on several days. However, mean systolic BP levels in a subsample with a 24-h ambulatory recording during medication showed similar results. This finding also indicated that medication for elevated BP could not mask the effect of birth size on systolic BP levels in hypertensive subjects.

Exercise habits are difficult to measure and no globally acceptable methods exist. For internal comparisons in this sample, we used two questions and a questionnaire by which subjects were divided into two groups according to their physical activity. Since exercise and physical activity habits, and consequently questionnaires, are culture dependent, we used the KIHD questionnaire validated in Finland (214), although only in men who were younger than the men in our study. The 12-month questionnaire has a representative time frame and a relatively small intra-person variability and is therefore suitable for the assessment of leisure time physical activity. All methods gave comparable results.

Body composition was measured by bioelectrical impedance analysis (BIA). The eight-polar BIA has been shown to give accurate estimates of body components in different populations without the need for population-specific algorithms (216-219). This method is practical in large epidemiological studies with limited time for examination of each subject (216; 217).

An obvious challenge for all body composition studies is that absolute measures such as lean or fat mass represent not only the proportion of that compartment but also body size itself. Birth weight is known to be related with adult body size: the heavier the newborn, the higher the height and BMI in adulthood (143; 188-192). In Study IV, we addressed this problem by adjusting analyses for adult height, which is closely related to the amount of lean mass, or BMI, which represents both lean and fat mass. In Study V we used height-normalized indices of adult lean and fat mass (221; 222). Age was included in these models since fat mass tends to increase and lean mass to decrease with age, even when weight remains stable (262). The association between high birth weight or BMI and greater lean mass in adulthood persisted independently of these adjustments. Thus, birth weight predicts lean body mass even within adults of the same sex and height or BMI.

7 CONCLUSIONS

The findings in the thesis studies illustrate the complex nature of the developmental origins of adult health and disease. A particular gene polymorphism, established hypertension, childhood growth pattern and adult habitual physical activity level were shown to modify the associations between early growth and the adult outcome. This may help to explain why some people with adverse experiences during early life, as indicated by small birth size or poor growth in infancy, develop e.g. hypertension or diabetes while other people with corresponding early predisposition are protected from the actual disease. In addition to early growth, another common theme in these studies was insulin resistance: blood pressure regulation, PPARγ2 gene Pro12Ala polymorphism, glucose tolerance, exercise habits, absolute and relative amounts of lean and fat body mass are all related to insulin sensitivity, which plays a major role in the development of the metabolic syndrome.

Among elderly men and women with established hypertension, size at birth had a strong effect on systolic BP levels whereas there was no relationship in people without hypertension. This finding illuminates the paradox that the negative association between birth weight and systolic BP is in general small, 2-4 mmHg in elderly subjects, while the low birth weight -related risk of hypertensive disease is substantial. Pathological features of BP regulation, originated during fetal life, are suggested to become self-perpetuating in adult life, eventually leading to hypertension. The highest systolic BP levels in hypertensive people were predicted by prevailing Pro12Pro polymorphism of the PPARγ2 gene together with low birth weight, indicating gene-environment interactions on BP levels that originate during fetal life. Because both the Pro12Pro genotype and low birth weight, individually and specifically in combination, have been related with higher insulin resistance, this mechanism may operate in the development of hypertension of an early origin. An interaction with the renin-angiotensin-aldosterone system is suggested by the finding that the hypertensive people with the Pro12Pro genotype and low birth weight were more likely to be receiving ACEI/ARB treatment.

Habitual physical activity protected elderly men and women who were small at birth, and thus at increased risk for the development of type 2 diabetes, against glucose intolerance more strongly. Regular physical activity at a modest level may alleviate or eliminate metabolic consequences that are related to small birth size. The importance of this is further highlighted by the finding that sufficient exercise intensity was comparable to brisk walking and thus achievable by most people. The studies on early growth in relation to adult body composition suggested that rapid gain in BMI before the age of 2 years promotes an increase in adult lean body mass

without excess fat accumulation whereas rapid gain in BMI in later childhood, despite the concurrent rise in lean mass, results in a relatively larger increase in fat mass. These findings constitute a rationale for future intervention studies.

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9 REFERENCES

1. Barker DJP: *Mothers, babies and health in later life*. Edinburgh, Churchill Livingstone, 1998

2. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. April 14, 2005 http://www.idf.org/webdata/docs/Metac_syndrome_def.pdf.

3. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005

4. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ: Weight in infancy and death from ischaemic heart disease. *Lancet* 2:577-580, 1989

5. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 36:62-67, 1993

6. Barker DJ, Osmond C, Simmonds SJ, Wield GA: The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *Bmj* 306:422-426, 1993

7. Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, Meade TW: Fetal and infant growth and cardiovascular risk factors in women. *Bmj* 310:428-432, 1995

8. Law CM, Barker DJ, Bull AR, Osmond C: Maternal and fetal influences on blood pressure. *Arch Dis Child* 66:1291-1295, 1991

9. Kramer MS, Joseph KS: Enigma of fetal/infant-origins hypothesis. *Lancet* 348:1254-1255, 1996

10. Paneth N, Susser M: Early origin of coronary heart disease (the "Barker hypothesis"). *Bmj* 310:411-412, 1995

11. Huxley R, Neil A, Collins R: Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* 360:659-665, 2002

12. Koupilova I, Leon DA, Lithell HO, Berglund L: Size at birth and hypertension in longitudinally followed 50-70-year-old men. *Blood Press* 6:223-228, 1997

13. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ: Early growth and coronary heart disease in later life: longitudinal study. *Bmj* 322:949-953, 2001

14. Forsén T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ: Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. *Bmj* 319:1403-1407, 1999

15. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD: Birthweight, body-mass index in middle age, and incident coronary heart disease. *Lancet* 348:1478-1480, 1996

16. Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, Lithell UB, McKeigue PM: Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *Bmj* 317:241-245, 1998

17. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, Willett WC, Hennekens CH: Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *Bmj* 315:396-400, 1997

18. Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ: Fetal growth and coronary heart disease in south India. *Lancet* 348:1269-1273, 1996

19. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. *Bmj* 312:406-410, 1996

20. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, Speizer FE, Manson JE: Birthweight and the risk for type 2 diabetes mellitus in adult women. *Ann Intern Med* 130:278-284, 1999

21. Cooper C, Eriksson JG, Forsen T, Osmond C, Tuomilehto J, Barker DJ: Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos Int* 12:623-629, 2001

22. Cheung YB, Khoo KS, Karlberg J, Machin D: Association between psychological symptoms in adults and growth in early life: longitudinal follow up study. *Bmj* 325:749, 2002

23. Paile-Hyvärinen M, Räikkönen K, Forsén T, Kajantie E, Ylihärsilä H, Salonen MK, Osmond C, Eriksson JG: Depression and its association with diabetes, cardiovascular disease, and birth weight. *Ann Med*:1-7, 2007

24. Räikkönen K, Pesonen AK, Kajantie E, Heinonen K, Forsén T, Phillips DI, Osmond C, Barker DJ, Eriksson JG: Length of gestation and depressive symptoms at age 60 years. *Br J Psychiatry* 190:469-474, 2007

25. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M: Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry* 69:178-182, 2008

26. McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CW, Miranda A, Fulgosi D, Kennedy SH: Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"? *Ann Clin Psychiatry* 19:257-264, 2007

27. Wahlbeck K, Forsen T, Osmond C, Barker DJ, Eriksson JG: Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. *Arch Gen Psychiatry* 58:48-52, 2001

28. Gunnell D, Harrison G, Whitley E, Lewis G, Tynelius P, Rasmussen F: The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women. *Schizophr Res* 79:315-322, 2005

29. Kajantie E, Phillips DI, Osmond C, Barker DJ, Forsen T, Eriksson JG: Spontaneous hypothyroidism in adult women is predicted by small body size at birth and during childhood. *J Clin Endocrinol Metab* 91:4953-4956, 2006

30. Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, Zitting P, Patel S, Little MP, Järvelin MR: Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax* 62:396-402, 2007

31. McCormack VA, dos Santos Silva I, Koupil I, Leon DA, Lithell HO: Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *Int J Cancer* 115:611-617, 2005

32. Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C, Barker DJ: Tallness and overweight during childhood have opposing effects on breast cancer risk. *Br J Cancer* 85:1680-1684, 2001

33. Gluckman P, Hanson, MA.: *The Fetal Matrix: evolution, development, and disease.* Cambridge, Cambridge University Press, 2004

34. Gilbert SF: Mechanisms for the environmental regulation of gene expression: ecological aspects of animal development. *J Biosci* 30:65-74, 2005

35. Deeming DC, Ferguson MW: Environmental regulation of sex determination in reptiles. *Philos Trans R Soc Lond B Biol Sci* 322:19-39, 1988

36. Ferguson MW, Joanen T: Temperature of egg incubation determines sex in Alligator mississippiensis. *Nature* 296:850-853, 1982

37. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP: Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 351:173-177, 1998

38. Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Schroeder-Tanka JM, van Montfrans GA, Michels RP, Bleker OP: Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart* 84:595-598, 2000

39. Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP: Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol Cell Endocrinol* 185:93-98, 2001

40. Gluckman PD, Hanson MA, Spencer HG, Bateson P: Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proc Biol Sci* 272:671-677, 2005

41. Lucas A, Fewtrell MS, Cole TJ: Fetal origins of adult disease-the hypothesis revisited. *Bmj* 319:245-249, 1999

42. Anway MD, Rekow SS, Skinner MK: Transgenerational epigenetic programming of the embryonic testis transcriptome. *Genomics*, 2007

43. Drake AJ, Walker BR, Seckl JR: Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. *Am J Physiol Regul Integr Comp Physiol* 288:R34-38, 2005

44. Eriksson JG: Epidemiology, genes and the environment: lessons learned from the Helsinki Birth Cohort Study. *J Intern Med* 261:418-425, 2007

45. Bogdarina I, Welham S, King PJ, Burns SP, Clark AJ: Epigenetic modification of the renin-angiotensin system in the fetal programming of hypertension. *Circ Res* 100:520-526, 2007

46. Weaver IC: Epigenetic programming by maternal behavior and pharmacological intervention. Nature versus nurture: let's call the whole thing off. *Epigenetics* 2:22-28, 2007

47. Kajantie E: Mechanisms of growth in small preterm infants and early life origins of adult cardiovascular disease. University of Helsinki, 2003

48. Dunkel L: Lastenendokrinologien käsikirja, 2005. http://www.lastenendokrinologit.net/kirja/index.html

49. Karlberg J, Jalil F, Lam B, Low L, Yeung CY: Linear growth retardation in relation to the three phases of growth. *Eur J Clin Nutr* 48 Suppl 1:S25-43; discussion S43-24, 1994

50. Gamborg M, Byberg L, Rasmussen F, Andersen PK, Baker JL, Bengtsson C, Canoy D, Droyvold W, Eriksson JG, Forsen T, Gunnarsdottir I, Järvelin MR, Koupil I, Lapidus L, Nilsen TI, Olsen SF, Schack-Nielsen L, Thorsdottir I, Tuomainen TP, Sörensen TI: Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol* 166:634-645, 2007

51. Phillips DI: Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment? *J Intern Med* 261:453-460, 2007

52. Gluckman PD, Hanson MA: Maternal constraint of fetal growth and its consequences. *Semin Fetal Neonatal Med* 9:419-425, 2004

53. Kirchengast S, Hartmann B: Impact of maternal age and maternal somatic characteristics on newborn size. *Am J Hum Biol* 15:220-228, 2003

54. Ounsted M, Scott A, Moar VA: Constrained and unconstrained fetal growth: associations with some biological and pathological factors. *Ann Hum Biol* 15:119-129, 1988

55. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB: Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. *Pediatr Res* 52:863-867, 2002

56. Drake AJ, Walker BR: The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol* 180:1-16, 2004

57. Tanner J: Growth as a target-seeking function: catch-up and catch-down growth in man. In *Human growth: a comprehensive treatise,* 2nd ed. Falkner F, Ed. New York, Plenum Press, 1986, p. 167-179

58. Karlberg J, Albertsson-Wikland K: Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res* 38:733-739, 1995

59. Ezzahir N, Alberti C, Deghmoun S, Zaccaria I, Czernichow P, Levy-Marchal C, Jaquet D: Time course of catch-up in adiposity influences adult anthropometry in individuals who were born small for gestational age. *Pediatr Res* 58:243-247, 2005

60. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB: Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *Bmj* 320:967-971, 2000

61. Kuh DL, Power C, Rodgers B: Secular trends in social class and sex differences in adult height. *Int J Epidemiol* 20:1001-1009, 1991

62. Hindmarsh PC, Geary MP, Rodeck CH, Kingdom JC, Cole TJ: Factors Predicting Ante- and Postnatal Growth. *Pediatr Res*, 2007

63. Cianfarani S, Germani D, Branca F: Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. *Arch Dis Child Fetal Neonatal Ed* 81:F71-73, 1999

64. Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG: Trajectories of growth among children who have coronary events as adults. *N Engl J Med* 353:1802-1809, 2005

65. Eriksson JG, Osmond C, Kajantie E, Forsén TJ, Barker DJ: Patterns of growth among children who later develop type 2 diabetes or its risk factors. *Diabetologia* 49:2853-2858, 2006

66. Singhal A, Cole TJ, Fewtrell M, Kennedy K, Stephenson T, Elias-Jones A, Lucas A: Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? *Circulation* 115:213-220, 2007

67. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A: Is slower early growth beneficial for long-term cardiovascular health? *Circulation* 109:1108-1113, 2004

68. Stettler N, Stallings VA, Troxel AB, Zhao J, Schinnar R, Nelson SE, Ziegler EE, Strom BL: Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 111:1897-1903, 2005

69. Ekelund U, Ong KK, Linne Y, Neovius M, Brage S, Dunger DB, Wareham NJ, Rossner S: Association of weight gain in infancy and early childhood with metabolic risk in young adults. *J Clin Endocrinol Metab* 92:98-103, 2007

70. Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, Ness AR, Dunger DB: Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. *Diabetologia* 47:1064-1070, 2004

71. Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, Biswas SK, Ramji S, Prabhakaran D, Reddy KS: Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med* 350:865-875, 2004

72. Barker DJ, Forsen T, Eriksson JG, Osmond C: Growth and living conditions in childhood and hypertension in adult life: a longitudinal study. *J Hypertens* 20:1951-1956, 2002

73. Adair LS, Cole TJ: Rapid child growth raises blood pressure in adolescent boys who were thin at birth. *Hypertension* 41:451-456, 2003

74. Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, Martyn CN, de Swiet M: Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. *Circulation* 105:1088-1092, 2002

75. Jaquet D, Deghmoun S, Chevenne D, Collin D, Czernichow P, Levy-Marchal C: Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. *Diabetologia* 48:849-855, 2005

76. Lundgren EM, Cnattingius HM, Jonsson GB, Tuvemo TH: Linear catch-up growth does not increase the risk of elevated blood pressure and reduces the risk of overweight in males. *J Hypertens* 19:1533-1538, 2001

77. Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM: Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Arch Dis Child* 92:109-114, 2007

78. Hales CN, Barker DJ: Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35:595-601, 1992

79. Lucas A: Role of nutritional programming in determining adult morbidity. *Arch Dis Child* 71:288-290, 1994

80. Bertram CE, Hanson MA: Animal models and programming of the metabolic syndrome. *Br Med Bull* 60:103-121, 2001

81. McMillen IC, Robinson JS: Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 85:571-633, 2005

82. Painter RC, de Rooij SR, Bossuyt PM, Simmers TA, Osmond C, Barker DJ, Bleker OP, Roseboom TJ: Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr* 84:322-327; quiz 466-327, 2006

83. Stein AD, Zybert PA, van der Pal-de Bruin K, Lumey LH: Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. *Eur J Epidemiol* 21:759-765, 2006

84. Roseboom TJ, van der Meulen JH, Ravelli AC, van Montfrans GA, Osmond C, Barker DJ, Bleker OP: Blood pressure in adults after prenatal exposure to famine. *J Hypertens* 17:325-330, 1999

85. Stein AD, Zybert PA, van de Bor M, Lumey LH: Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. *Int J Epidemiol* 33:831-836, 2004

86. Stanner SA, Yudkin JS: Fetal programming and the Leningrad Siege study. *Twin Res* 4:287-292, 2001

87. Räikkönen K a, Kajantie E, Rautanen A, Eriksson JG: Metabolic syndrome. In *Handbook of research methods in health psychology* Luecken LJ a, Gallo LC, Ed., SAGE Publications, Thousand Oaks, 2008, p. 299-322

88. Björntorp P: Insulin resistance: the consequence of a neuroendocrine disturbance? *Int J Obes Relat Metab Disord* 19 Suppl 1:S6-10, 1995

89. Kajantie E, Feldt K, Raikkonen K, Phillips DI, Osmond C, Heinonen K, Pesonen AK, Andersson S, Barker DJ, Eriksson JG: Body size at birth predicts hypothalamic-pituitary-adrenal axis response to psychosocial stress at age 60 to 70 years. *J Clin Endocrinol Metab* 92:4094-4100, 2007

90. Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, Barker DJ, Whorwood CB: Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension* 35:1301-1306, 2000

91. Phillips DI, Jones A, Goulden PA: Birth weight, stress, and the metabolic syndrome in adult life. *Ann N Y Acad Sci* 1083:28-36, 2006

92. Reynolds RM, Godfrey KM, Barker M, Osmond C, Phillips DI: Stress responsiveness in adult life: influence of mother's diet in late pregnancy. *J Clin Endocrinol Metab* 92:2208-2210, 2007

93. Seckl JR: Glucocorticoids, feto-placental 11 beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. *Steroids* 62:89-94, 1997

94. Everson SA, Kaplan GA, Goldberg DE, Salonen JT: Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. *Hypertension* 27:1059-1064, 1996

95. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen R, Salonen JT: Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. *Circulation* 96:3842-3848, 1997

96. Painter RC, de Rooij SR, Bossuyt PM, Phillips DI, Osmond C, Barker DJ, Bleker OP, Roseboom TJ: Blood pressure response to psychological stressors in adults after prenatal exposure to the Dutch famine. *J Hypertens* 24:1771-1778, 2006

97. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171-175, 1994

98. Mackenzie HS, Lawler EV, Brenner BM: Congenital oligonephropathy: The fetal flaw in essential hypertension? *Kidney Int Suppl* 55:S30-34, 1996

99. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I: Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 58:770-773, 2000

100. Hughson M, Farris AB, 3rd, Douglas-Denton R, Hoy WE, Bertram JF: Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int* 63:2113-2122, 2003

101. Chen Y, Lasaitiene D, Friberg P: The renin-angiotensin system in kidney development. *Acta Physiol Scand* 181:529-535, 2004

102. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips DI: Reduced foetal growth and growth hormone secretion in adult life. *Clin Endocrinol (Oxf)* 50:735-740, 1999

103. Martyn CN, Greenwald SE: Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet* 350:953-955, 1997

104. Martin H, Gazelius B, Norman M: Impaired acetylcholine-induced vascular relaxation in low birth weight infants: implications for adult hypertension? *Pediatr Res* 47:457-462, 2000

105. Gale CR, Jiang B, Robinson SM, Godfrey KM, Law CM, Martyn CN: Maternal diet during pregnancy and carotid intima-media thickness in children. *Arterioscler Thromb Vasc Biol* 26:1877-1882, 2006

106. Goodfellow J, Bellamy MF, Gorman ST, Brownlee M, Ramsey MW, Lewis MJ, Davies DP, Henderson AH: Endothelial function is impaired in fit young adults of low birth weight. *Cardiovasc Res* 40:600-606, 1998

107. Ozanne SE, Jensen CB, Tingey KJ, Storgaard H, Madsbad S, Vaag AA: Low birthweight is associated with specific changes in muscle insulin-signalling protein expression. *Diabetologia* 48:547-552, 2005

108. Thompson CH, Sanderson AL, Sandeman D, Stein C, Borthwick A, Radda GK, Phillips DI: Fetal growth and insulin resistance in adult life: role of skeletal muscle morphology. *Clin Sci (Lond)* 92:291-296, 1997

109. Taylor DJ, Thompson CH, Kemp GJ, Barnes PR, Sanderson AL, Radda GK, Phillips DI: A relationship between impaired fetal growth and reduced muscle glycolysis revealed by 31P magnetic resonance spectroscopy. *Diabetologia* 38:1205-1212, 1995

110. Phillips DI: Relation of fetal growth to adult muscle mass and glucose tolerance. *Diabet Med* 12:686-690, 1995

111. Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL: Body composition in appropriate and in small for gestational age infants. *Acta Paediatr* 86:196-200, 1997

112. Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW: Muscularity and fatness of infants and young children born small- or large-for-gestational-age. *Pediatrics* 102:E60, 1998

113. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A: Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? *Am J Clin Nutr* 77:726-730, 2003

114. Eriksson J, Forsén T, Tuomilehto J, Osmond C, Barker D: Size at birth, fat-free mass and resting metabolic rate in adult life. *Horm Metab Res* 34:72-76, 2002

115. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C: Intrauterine programming of adult body composition. *J Clin Endocrinol Metab* 86:267-272, 2001

116. Sayer AA, Syddall HE, Dennison EM, Gilbody HJ, Duggleby SL, Cooper C, Barker DJ, Phillips DI: Birth weight, weight at 1 y of age, and body composition in older men: findings from the Hertfordshire Cohort Study. *Am J Clin Nutr* 80:199-203, 2004

117. Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M: Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *Am J Clin Nutr* 82:980-987, 2005

118. Dulloo AG, Jacquet J, Montani JP: Pathways from weight fluctuations to metabolic diseases: focus on maladaptive thermogenesis during catch-up fat. *Int J Obes Relat Metab Disord* 26 Suppl 2:S46-57, 2002

119. Levy-Marchal C, Jaquet D, Czernichow P: Long-term metabolic consequences of being born small for gestational age. *Semin Neonatol* 9:67-74, 2004

120. Martins PA, Hoffman DJ, Fernandes MT, Nascimento CR, Roberts SB, Sesso R, Sawaya AL: Stunted children gain less lean body mass and more fat mass than their non-stunted counterparts: a prospective study. *Br J Nutr* 92:819-825, 2004

121. Dulloo AG, Jacquet J, Seydoux J, Montani JP: The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. *Int J Obes (Lond)* 30 Suppl 4:S23-35, 2006

122. Reik W, Constancia M, Fowden A, Anderson N, Dean W, Ferguson-Smith A, Tycko B, Sibley C: Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *J Physiol* 547:35-44, 2003

123. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD: Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol Endocrinol Metab* 279:E83-87, 2000

124. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539-553, 1998

125. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 365:1415-1428, 2005

126. Eriksson J, Forsén T, Tuomilehto J, Osmond C, Barker D: Fetal and childhood growth and hypertension in adult life. *Hypertension* 36:790-794, 2000

127. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *Bmj* 303:1019-1022, 1991

128. Yarbrough DE, Barrett-Connor E, Kritz-Silverstein D, Wingard DL: Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. *Diabetes Care* 21:1652-1658, 1998

129. Kajantie E, Barker DJ, Osmond C, Forsen T, Eriksson JG: Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort Study. *Int J Epidemiol*, 2008

130. Laaksonen DE, Lakka HM, Lynch J, Lakka TA, Niskanen L, Rauramaa R, Salonen JT, Kauhanen J: Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. *Diabetes Care* 26:2156-2164, 2003

131. Ramadhani MK, Grobbee DE, Bots ML, Castro Cabezas M, Vos LE, Oren A, Uiterwaal CS: Lower birth weight predicts metabolic syndrome in young adults: the Atherosclerosis Risk in Young Adults (ARYA)-study. *Atherosclerosis* 184:21-27, 2006

132. de Rooij SR, Painter RC, Holleman F, Bossuyt PM, Roseboom TJ: The metabolic syndrome in adults prenatally exposed to the Dutch famine. *Am J Clin Nutr* 86:1219-1224, 2007

133. te Velde SJ, Twisk JW, van Mechelen W, Kemper HC: A birth-weight questionnaire indicated that life style modifies the birth weight and metabolic syndrome relationship at age 36. *J Clin Epidemiol* 58:1172-1179, 2005

134. Parker L, Lamont DW, Unwin N, Pearce MS, Bennett SM, Dickinson HO, White M, Mathers JC, Alberti KG, Craft AW: A lifecourse study of risk for hyperinsulinaemia, dyslipidaemia and obesity (the central metabolic syndrome) at age 49-51 years. *Diabet Med* 20:406-415, 2003

135. Vanhala MJ, Vanhala PT, Keinanen-Kiukaanniemi SM, Kumpusalo EA, Takala JK: Relative weight gain and obesity as a child predict metabolic syndrome as an adult. *Int J Obes Relat Metab Disord* 23:656-659, 1999

136. Huang TT, Nansel TR, Belsheim AR, Morrison JA: Sensitivity, specificity, and predictive values of pediatric metabolic syndrome components in relation to adult metabolic syndrome: the Princeton LRC follow-up study. *J Pediatr* 152:185-190, 2008

137. Fagerberg B, Bondjers L, Nilsson P: Low birth weight in combination with catch-up growth predicts the occurrence of the metabolic syndrome in men at late middle age: the Atherosclerosis and Insulin Resistance study. *J Intern Med* 256:254-259, 2004

138. Morrison JA, Friedman LA, Wang P, Glueck CJ: Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr* 152:201-206, 2008

139. Vanhala M, Vanhala P, Kumpusalo E, Halonen P, Takala J: Relation between obesity from childhood to adulthood and the metabolic syndrome: population based study. *Bmj* 317:319, 1998

140. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS: Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. *Pediatrics* 108:712-718, 2001

141. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempe M, Guilloud-Bataille M, Patois E: Adiposity rebound in children: a simple indicator for predicting obesity. *Am J Clin Nutr* 39:129-135, 1984

142. Dietz WH: Critical periods in childhood for the development of obesity. *Am J Clin Nutr* 59:955-959, 1994

143. Eriksson J, Forsén T, Osmond C, Barker D: Obesity from cradle to grave. *Int J Obes Relat Metab Disord* 27:722-727, 2003

144. Bouhours-Nouet N, Dufresne S, de Casson FB, Mathieu E, Douay O, Gatelais F, Rouleau S, Coutant R: High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? *Diabetes Care* 31:1031-1036, 2008

145. Law CM, Shiell AW: Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens* 14:935-941, 1996

146. Huxley RR, Shiell AW, Law CM: The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* 18:815-831, 2000

147. Tu YK, West R, Ellison GT, Gilthorpe MS: Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life. *Am J Epidemiol* 161:27-32, 2005

148. Schluchter MD: Publication bias and heterogeneity in the relationship between systolic blood pressure, birth weight, and catch-up growth--a meta analysis. *J Hypertens* 21:273-279, 2003

149. Cruickshank JK, Beith C, Koudsi A: Unravelling the fetal origins hypothesis. *Lancet* 360:2073-2074; author reply 2074-2075, 2002

150. Barker DJ, Eriksson JG, Forsen T, Osmond C: Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* 31:1235-1239, 2002

151. Eriksson JG, Forsen T: Unravelling the fetal origins hypothesis. *Lancet* 360:2072; author reply 2074-2075, 2002

152. Järvelin MR, Sovio U, King V, Lauren L, Xu B, McCarthy MI, Hartikainen AL, Laitinen J, Zitting P, Rantakallio P, Elliott P: Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. *Hypertension* 44:838-846, 2004

153. Hardy R, Sovio U, King VJ, Skidmore PM, Helmsdal G, Olsen SF, Emmett PM, Wadsworth ME, Jarvelin MR: Birthweight and blood pressure in five European birth cohort studies: an investigation of confounding factors. *Eur J Public Health* 16:21-30, 2006

154. Law CM, de Swiet M, Osmond C, Fayers PM, Barker DJ, Cruddas AM, Fall CH: Initiation of hypertension in utero and its amplification throughout life. *Bmj* 306:24-27, 1993

155. Hardy R, Kuh D, Langenberg C, Wadsworth ME: Birthweight, childhood social class, and change in adult blood pressure in the 1946 British birth cohort. *Lancet* 362:1178-1183, 2003

156. Koupil I, Leon DA, Byberg L: Birth weight, hypertension and "white coat" hypertension: size at birth in relation to office and 24-h ambulatory blood pressure. *J Hum Hypertens* 19:635-642, 2005

157. Lackland DT, Egan BM, Syddall HE, Barker DJ: Associations between birth weight and antihypertensive medication in black and white medicaid recipients. *Hypertension* 39:179-183, 2002

158. Cole TJ: Modeling postnatal exposures and their interactions with birth size. *J Nutr* 134:201-204, 2004

159. Head RF, Tu YK, Gilthorpe MS, Mishra GD, Williams S, Ellison GT: What evidence is there that adjustment for adult height influences the relationship between birth weight and blood pressure? *Ann Hum Biol* 34:252-264, 2007

160. Stumvoll M, Häring H: The peroxisome proliferator-activated receptor-gamma2 Pro12Ala polymorphism. *Diabetes* 51:2341-2347, 2002

161. Debril MB, Renaud JP, Fajas L, Auwerx J: The pleiotropic functions of peroxisome proliferator-activated receptor gamma. *J Mol Med* 79:30-47, 2001

162. Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR: Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 241:270-274, 1997

163. Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J: A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20:284-287, 1998

164. Eriksson JG, Lindi V, Uusitupa M, Forsén TJ, Laakso M, Osmond C, Barker DJ: The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 51:2321-2324, 2002

165. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN: Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 33:177-182, 2003

166. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES: The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76-80, 2000

167. Meirhaeghe A, Amouyel P: Impact of genetic variation of PPARgamma in humans. *Mol Genet Metab* 83:93-102, 2004

168. Tönjes A, Scholz M, Loeffler M, Stumvoll M: Association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma with Pre-diabetic phenotypes: meta-analysis of 57 studies on nondiabetic individuals. *Diabetes Care* 29:2489-2497, 2006

169. Ludovico O, Pellegrini F, Di Paola R, Minenna A, Mastroianno S, Cardellini M, Marini MA, Andreozzi F, Vaccaro O, Sesti G, Trischitta V: Heterogeneous effect of peroxisome proliferator-activated receptor gamma2 Ala12 variant on type 2 diabetes risk. *Obesity (Silver Spring)* 15:1076-1081, 2007

170. Stumvoll M, Stefan N, Fritsche A, Madaus A, Tschritter O, Koch M, Machicao F, Haring H: Interaction effect between common polymorphisms in PPARgamma2 (Pro12Ala) and insulin receptor substrate 1 (Gly972Arg) on insulin sensitivity. *J Mol Med* 80:33-38, 2002

171. Jaquet D, Tregouet DA, Godefroy T, Nicaud V, Chevenne D, Tiret L, Czernichow P, Levy-Marchal C, Gaboriau A: Combined effects of genetic and environmental factors on insulin resistance associated with reduced fetal growth

Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. *Diabetes* 51:3473-3478, 2002

172. Bosse Y, Weisnagel SJ, Bouchard C, Despres JP, Perusse L, Vohl MC: Combined effects of PPARgamma2 P12A and PPARalpha L162V polymorphisms on glucose and insulin homeostasis: the Quebec Family Study. *J Hum Genet* 48:614-621, 2003

173. Franks PW, Luan J, Browne PO, Harding AH, O'Rahilly S, Chatterjee VK, Wareham NJ: Does peroxisome proliferator-activated receptor gamma genotype (Pro12ala) modify the association of physical activity and dietary fat with fasting insulin level? *Metabolism* 53:11-16, 2004

174. de Rooij SR, Painter RC, Phillips DI, Osmond C, Tanck MW, Defesche JC, Bossuyt PM, Michels RP, Bleker OP, Roseboom TJ: The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene on glucose/insulin metabolism interact with prenatal exposure to famine. *Diabetes Care* 29:1052-1057, 2006

175. Knouff C, Auwerx J: Peroxisome proliferator-activated receptor-gamma calls for activation in moderation: lessons from genetics and pharmacology. *Endocr Rev* 25:899-918, 2004

176. Hasstedt SJ, Ren QF, Teng K, Elbein SC: Effect of the peroxisome proliferator-activated receptor-gamma 2 pro(12)ala variant on obesity, glucose homeostasis, and blood pressure in members of familial type 2 diabetic kindreds. *J Clin Endocrinol Metab* 86:536-541, 2001

177. Ostgren CJ, Lindblad U, Melander O, Melander A, Groop L, Råstam L: Peroxisome proliferator-activated receptor-gammaPro12Ala polymorphism and the association with blood pressure in type 2 diabetes: skaraborg hypertension and diabetes project. *J Hypertens* 21:1657-1662, 2003

178. Stefanski A, Majkowska L, Ciechanowicz A, Frankow M, Safranow K, Parczewski M, Moleda P, Pilarska K: Association between the Pro12Ala variant of the peroxisome proliferator-activated receptor-gamma2 gene and increased 24-h diastolic blood pressure in obese patients with type II diabetes. *J Hum Hypertens* 20:684-692, 2006

179. Vaccaro O, Mancini FP, Ruffa G, Sabatino L, Iovine C, Masulli M, Colantuoni V, Riccardi G: Fasting plasma free fatty acid concentrations and Pro12Ala polymorphism of the peroxisome proliferator-activated receptor (PPAR) gamma2 gene in healthy individuals. *Clin Endocrinol (Oxf)* 57:481-486, 2002

180. Gouni-Berthold I, Giannakidou E, Muller-Wieland D, Faust M, Kotzka J, Berthold HK, Krone W: Peroxisome proliferator-activated receptor-gamma2 Pro12Ala and endothelial nitric oxide synthase-4a/b gene polymorphisms are not associated with hypertension in diabetes mellitus type 2. *J Hypertens* 23:301-308, 2005

181. Rodriguez-Esparragon FJ, Rodriguez-Perez JC, Macias-Reyes A, Alamo-Santana F: Peroxisome proliferator-activated receptor-gamma2-Pro12Ala and endothelial nitric oxide synthase-4a/bgene polymorphisms are associated with essential hypertension. *J Hypertens* 21:1649-1655, 2003

182. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A: Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* 165:849-857, 2007

183. Silverman BL, Metzger BE, Cho NH, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to fetal hyperinsulinism. *Diabetes Care* 18:611-617, 1995

184. Lakka TA, Laaksonen DE: Physical activity in prevention and treatment of the metabolic syndrome. *Appl Physiol Nutr Metab* 32:76-88, 2007

185. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343-1350, 2001

186. Boreham CA, Murray L, Dedman D, Davey Smith G, Savage JM, Strain JJ: Birthweight and aerobic fitness in adolescents: the Northern Ireland Young Hearts Project. *Public Health* 115:373-379, 2001

187. Demura S, Sato S, Kitabayashi T: Percentage of total body fat as estimated by three automatic bioelectrical impedance analyzers. *J Physiol Anthropol Appl Human Sci* 23:93-99, 2004

188. Charney E, Goodman HC, McBride M, Lyon B, Pratt R: Childhood antecedents of adult obesity. Do chubby infants become obese adults? *N Engl J Med* 295:6-9, 1976

189. Oken E, Gillman MW: Fetal origins of obesity. *Obes Res* 11:496-506, 2003

190. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ: Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 94:3246-3250, 1996

191. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ: Birth weight and adult hypertension and obesity in women. *Circulation* 94:1310-1315, 1996

192. Rasmussen F, Johansson M: The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *Eur J Epidemiol* 14:373-380, 1998

193. Eriksson JG, Forsén TJ, Osmond C, Barker DJ: Pathways of infant and childhood growth that lead to type 2 diabetes. *Diabetes Care* 26:3006-3010, 2003

194. Eriksson JG, Forsén T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ: Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 45:342-348, 2002

195. Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C: Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. *J Clin Endocrinol Metab* 85:1401-1406, 2000

196. Phillips DI, Barker DJ, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37:150-154, 1994

197. Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C: Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes* 48:2422-2429, 1999

198. Ong KK, Dunger DB: Birth weight, infant growth and insulin resistance. *Eur J Endocrinol* 151 Suppl 3:U131-139, 2004

199. Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G, Ong KK, Dunger DB, Mericq MV: Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. *J Clin Endocrinol Metab* 88:3645-3650, 2003

200. Veening MA, Van Weissenbruch MM, Delemarre-Van De Waal HA: Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab* 87:4657-4661, 2002

201. Whincup PH, Cook DG, Adshead F, Taylor SJ, Walker M, Papacosta O, Alberti KG: Childhood size is more strongly related than size at birth to glucose and insulin levels in 10-11-year-old children. *Diabetologia* 40:319-326, 1997

202. Byberg L, McKeigue PM, Zethelius B, Lithell HO: Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. *Diabetologia* 43:54-60, 2000

203. Garnett SP, Cowell CT, Baur LA, Fay RA, Lee J, Coakley J, Peat JK, Boulton TJ: Abdominal fat and birth size in healthy prepubertal children. *Int J Obes Relat Metab Disord* 25:1667-1673, 2001

204. Kuh D, Hardy R, Chaturvedi N, Wadsworth ME: Birth weight, childhood growth and abdominal obesity in adult life. *Int J Obes Relat Metab Disord* 26:40-47, 2002

205. Law CM, Barker DJ, Osmond C, Fall CH, Simmonds SJ: Early growth and abdominal fatness in adult life. *J Epidemiol Community Health* 46:184-186, 1992

206. Rogers IS, Ness AR, Steer CD, Wells JC, Emmett PM, Reilly JR, Tobias J, Smith GD: Associations of size at birth and dual-energy X-ray absorptiometry measures of lean and fat mass at 9 to 10 y of age. *Am J Clin Nutr* 84:739-747, 2006

207. Hng TM, McLean M, Cheung NW, Thompson CH: The interrelation of birth weight and regional lipid deposition: a twins study. *Metabolism* 55:561-562, 2006

208. Ibáñez L, Ong K, Dunger DB, de Zegher F: Early Development of Adiposity and Insulin Resistance Following Catch-up Weight Gain in Small-for-Gestational-Age Children. *J Clin Endocrinol Metab*, 2006

209. Wells JC, Hallal PC, Wright A, Singhal A, Victora CG: Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. *Int J Obes Relat Metab Disord*, 2005

210. Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R: Associations between prenatal and postnatal growth and adult body size and composition. *Am J Clin Nutr* 77:1498-1505, 2003

211. Ekelund U, Ong K, Linne Y, Neovius M, Brage S, Dunger DB, Wareham NJ, Rossner S: Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: the Stockholm Weight Development Study (SWEDES). *Am J Clin Nutr* 83:324-330, 2006

212. Sachdev HS, Fall CH, Osmond C, Lakshmy R, Dey Biswas SK, Leary SD, Reddy KS, Barker DJ, Bhargava SK: Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. *Am J Clin Nutr* 82:456-466, 2005

213. Victora CG, Sibbritt D, Horta BL, Lima RC, Cole T, Wells J: Weight gain in childhood and body composition at 18 years of age in Brazilian males. *Acta Paediatr* 96:296-300, 2007

214. Lakka TA, Salonen JT: Intra-person variability of various physical activity assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol* 21:467-472, 1992

215. *World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation: Part 1. Diagnosis and classification of diabetes mellitus.* Geneva, World Health Organization, 1999

216. Bedogni G, Malavolti M, Severi S, Poli M, Mussi C, Fantuzzi AL, Battistini N: Accuracy of an eight-point tactile-electrode impedance method in the assessment of total body water. *Eur J Clin Nutr* 56:1143-1148, 2002

217. Malavolti M, Mussi C, Poli M, Fantuzzi AL, Salvioli G, Battistini N, Bedogni G: Cross-calibration of eight-polar bioelectrical impedance analysis versus dual-energy X-ray absorptiometry for the assessment of total and appendicular body composition in healthy subjects aged 21-82 years. *Ann Hum Biol* 30:380-391, 2003

218. Sartorio A, Malavolti M, Agosti F, Marinone PG, Caiti O, Battistini N, Bedogni G: Body water distribution in severe obesity and its assessment from eight-polar bioelectrical impedance analysis. *Eur J Clin Nutr* 59:155-160, 2005

219. Gibson AL, Holmes JC, Desautels RL, Edmonds LB, Nuudi L: Ability of new octapolar bioimpedance spectroscopy analyzers to predict 4-component-model percentage body fat in Hispanic, black, and white adults. *Am J Clin Nutr* 87:332-338, 2008

220. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN: The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. *Pediatrics* 118:1486-1492, 2006

221. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA: Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* 52:953-959, 1990

222. Wells JC: A critique of the expression of paediatric body composition data. *Arch Dis Child* 85:67-72, 2001

223. World Health Organization. The WHO Child Growth Standards. In *Internet: http://www.who.int/childgrowth/standards/en/ (accessed May 2007)*

224. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH: Establishing a standard definition for child overweight and obesity worldwide: international survey. *Bmj* 320:1240-1243, 2000

225. Koupilova I, Leon DA, McKeigue PM, Lithell HO: Is the effect of low birth weight on cardiovascular mortality mediated through high blood pressure? *J Hypertens* 17:19-25, 1999

226. Merlet-Benichou C LB, Gilbert T, Lelievre-Pegorier M: Retard de croissance intra-uterin et deficit en nephrons [Intrauterine growth retardation and inborn nephron deficit]. *Medecine/Sciences* 9:777-780, 1993

227. Martyn CN, Greenwald S.E.: Mechanisms for in-utero programming of blood pressure. In *Fetal origins of cardiovascular and lung disease,* Barker, DJP ed. New York, Marcel Dekker, 2001

228. Nickenig G, Röling J, Strehlow K, Schnabel P, Böhm M: Insulin induces upregulation of vascular AT1 receptor gene expression by posttranscriptional mechanisms. *Circulation* 98:2453-2460, 1998

229. Velloso LA, Folli F, Sun XJ, White MF, Saad MJ, Kahn CR: Cross-talk between the insulin and angiotensin signaling systems. *Proc Natl Acad Sci U S A* 93:12490-12495, 1996

230. Velloso LA, Folli F, Perego L, Saad MJ: The multi-faceted cross-talk between the insulin and angiotensin II signaling systems. *Diabetes Metab Res Rev* 22:98-107, 2006

231. Sherman RC, Langley-Evans SC: Early administration of angiotensin-converting enzyme inhibitor captopril, prevents the development of hypertension programmed by intrauterine exposure to a maternal low-protein diet in the rat. *Clin Sci (Lond)* 94:373-381, 1998

232. Hattersley AT, Tooke JE: The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 353:1789-1792, 1999

233. Pihlajamäki J, Vanhala M, Vanhala P, Laakso M: The Pro12Ala polymorphism of the PPAR gamma 2 gene regulates weight from birth to adulthood. *Obes Res* 12:187-190, 2004

234. Pfab T, Poralla C, Richter CM, Godes M, Slowinski T, Priem F, Halle H, Hocher B: Fetal and maternal peroxisome proliferator-activated receptor gamma2 Pro12Ala does not influence birth weight. *Obesity (Silver Spring)* 14:1880-1885, 2006

235. Eriksson JG, Lindi V, Uusitupa M, Forsen TJ, Laakso M, Osmond C, Barker DJ: The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 51:2321-2324, 2002

236. Hermann TS, Rask-Madsen C, Ihlemann N, Dominguez H, Jensen CB, Storgaard H, Vaag AA, Kober L, Torp-Pedersen C: Normal insulin-stimulated endothelial function and impaired insulin-stimulated muscle glucose uptake in young adults with low birth weight. *J Clin Endocrinol Metab* 88:1252-1257, 2003

237. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774-778, 1991

238. Eriksson JG: Exercise and the treatment of type 2 diabetes mellitus. An update. *Sports Med* 27:381-391, 1999

239. Gill JM, Malkova D: Physical activity, fitness and cardiovascular disease risk in adults: interactions with insulin resistance and obesity. *Clin Sci (Lond)* 110:409-425, 2006

240. Sun SS, Liang R, Huang TT, Daniels SR, Arslanian S, Liu K, Grave GD, Siervogel RM: Childhood obesity predicts adult metabolic syndrome: the Fels Longitudinal Study. *J Pediatr* 152:191-200, 2008

241. Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ: Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 73:460-468, 1994

242. Sternfeld B, Ngo L, Satariano WA, Tager IB: Associations of body composition with physical performance and self-reported functional limitation in elderly men and women. *Am J Epidemiol* 156:110-121, 2002

243. Kuh D, Bassey J, Hardy R, Aihie Sayer A, Wadsworth M, Cooper C: Birth weight, childhood size, and muscle strength in adult life: evidence from a birth cohort study. *Am J Epidemiol* 156:627-633, 2002

244. Sayer AA, Syddall HE, Gilbody HJ, Dennison EM, Cooper C: Does sarcopenia originate in early life? Findings from the Hertfordshire cohort study. *J Gerontol A Biol Sci Med Sci* 59:M930-934, 2004

245. Lawlor DA, Davey Smith G, Ebrahim S: Life course influences on insulin resistance: findings from the British Women's Heart and Health Study. *Diabetes Care* 26:97-103, 2003

246. Hypponen E, Power C, Smith GD: Prenatal growth, BMI, and risk of type 2 diabetes by early midlife. *Diabetes Care* 26:2512-2517, 2003

247. Stein AD, Thompson AM, Waters A: Childhood growth and chronic disease: evidence from countries undergoing the nutrition transition. *Matern Child Nutr* 1:177-184, 2005

248. Rosen ED, Spiegelman BM: Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 444:847-853, 2006

249. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C: Being big or growing fast: systematic review of size and growth in infancy and later obesity. *Bmj* 331:929, 2005

250. Monteiro PO, Victora CG: Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev* 6:143-154, 2005

251. Stettler N, Zemel BS, Kumanyika S, Stallings VA: Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* 109:194-199, 2002

252. Demerath EW, Schubert CM, Maynard LM, Sun SS, Chumlea WC, Pickoff A, Czerwinski SA, Towne B, Siervogel RM: Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels Longitudinal Study. *Pediatrics* 117:e487-495, 2006

253. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET: Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 89:2569-2575, 2004

254. Després JP: Intra-abdominal obesity: an untreated risk factor for Type 2 diabetes and cardiovascular disease. *J Endocrinol Invest* 29:77-82, 2006

255. Salmenniemi U, Ruotsalainen E, Vanttinen M, Vauhkonen I, Pihlajamaki J, Kainulainen S, Punnonen K, Laakso M: High amount of visceral fat mass is associated with multiple metabolic changes in offspring of type 2 diabetic patients. *Int J Obes (Lond)* 29:1464-1470, 2005

256. Syddall H, Cooper C, Martin F, Briggs R, Aihie Sayer A: Is grip strength a useful single marker of frailty? *Age Ageing* 32:650-656, 2003

257. Population ageing: a looming public health challenge. *Health Millions* 24:20-22, 1998

258. Broadwin J, Goodman-Gruen D, Slymen D: Ability of fat and fat-free mass percentages to predict functional disability in older men and women. *J Am Geriatr Soc* 49:1641-1645, 2001

259. Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B: Mortality associated with body fat, fat-free mass and body mass index among 60-year-old swedish men-a 22-year follow-up. The study of men born in 1913. *Int J Obes Relat Metab Disord* 24:33-37, 2000

260. Strawbridge WJ, Cohen RD, Shema SJ, Kaplan GA: Successful aging: predictors and associated activities. *Am J Epidemiol* 144:135-141, 1996

261. Wells JC, Coward WA, Cole TJ, Davies PS: The contribution of fat and fat-free tissue to body mass index in contemporary children and the reference child. *Int J Obes Relat Metab Disord* 26:1323-1328, 2002

262. Gallagher D, Ruts E, Visser M, Heshka S, Baumgartner RN, Wang J, Pierson RN, Pi-Sunyer FX, Heymsfield SB: Weight stability masks sarcopenia in elderly men and women. *Am J Physiol Endocrinol Metab* 279:E366-375, 2000